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GLUCOSE DEFICIENCY AS A FACTOR IN THE PRODUCTION OF SYMPTOMS REFERABLE TO THE CARDIOVASCULAR SYSTEM

T. R. HARRISON, M.D., AND ROBERT M. FINKS, M.D.*
WINSTON-SALEM, N. C.

INTRODUCTION

Definition.—The purpose of this communication is to emphasize the relationship of certain disturbances of cardiovascular function to a metabolic disorder characterized by the following features: (1) The symptoms practically always occur two or more hours after meals; (2) they can usually be reproduced by the injection of insulin; (3) they can be relieved by the ingestion of glucose and—in large measure—prevented by dietary regulation; and (4) at the time the symptoms occur the level of the blood sugar is usually either slightly subnormal or within the lower limits of the normal range.

In designating this syndrome, the term "hyperinsulinism" has been avoided because there is evidence that in certain instances other mechanisms than an overproduction of insulin are involved. Moreover, since the values for "blood sugar" (which actually—as measured—represent the total reducing substances rather than the glucose content) are not, in all instances, definitely below the normal range, the phrases "glucose deficiency" and "relative hypoglycemia" are used rather than the unqualified term "hypoglycemia."

Since 1924, when Harris[1] described spontaneous hypoglycemia and named it hyperinsulinism, numerous publications dealing with this subject have appeared. Most of the authors have been interested in the cases of severe attacks of unconsciousness or convulsions, and relatively little attention has been paid to the milder symptoms. Having been impressed by the frequency of mild forms of relative hypoglycemia, and having observed that the symptoms are often referred to the cardiovascular system, we wish, in this report, to discuss the significance of this

From the Department of Internal Medicine of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.
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*At present Major, M.C., A.U.S.

condition in inducing attacks of a number of well-recognized cardiovascular syndromes.

We have observed thirty-one cases in which relative hypoglycemia appeared to be responsible for disturbances of cardiovascular function. In most of these patients this condition was not the chief disorder, and in several of them it was a purely incidental feature. However, glucose deficiency was frequently an important precipitating factor in various types of cardiovascular attacks, and occasionally it was the sole cause of the symptoms. A summary of the most important features of the thirty-one patients is presented in Table I.

TABLE I

CARDIOVASCULAR SYNDROMES OBSERVED IN THIRTY-ONE PATIENTS WITH SPONTANEOUS HYPOGLYCEMIA

		NUMBER OF PATIENTS	NERVOUSNESS	FRIGHT	WEAKNESS	PALPITATION	PAIN IN CHEST: NON-ANGINAL	PAIN IN CHEST: ANGINAL	DIZZINESS	DYSPNEA (SIGHING)	"CHOKING" FEELING	ARRHYTHMIAS	LOCAL PARESTHESIA	REMARKS
Entire group		31	25	13	23	17	9	6	9	8	3	7	2	
Group simulating cardiac neurosis*		14	14	9	14	10	8	0	5	8	3	0	0	7 of the patients had both cardiac neurosis and hypoglycemia
Arrhythmias	Premature beats	3	1	1	0	3	0	0	0	0	0	3	0	
	Paroxysmal tachycardia	3	3	2	3	3	1	0	0	0	0	3	0	Hypoglycemia one of several precipitating factors
	Paroxysmal auricular fibrillation	1	1	0	1	1	0	0	0	0	0	1	0	
Angina pectoris		6	3	1	2	0	0	6	0	0	0	0	0	Hypoglycemia a precipitating factor only, in 4 cases. Apparently sole factor in 2 cases
Hypersensitive carotid sinus		2	2	0	2	0	0	0	2	0	0	0	0	Hypoglycemia apparently one of several precipitating factors
Hypertensive encephalopathy		2	1	0	1	0	0	0	2	0	0	0	2	Hypoglycemia apparently the sole precipitating factor in one case; one of several factors in the other case

*Four of these patients had typical menopausal syndromes.

THE DIAGNOSIS OF RELATIVE HYPOGLYCEMIA

The decision as to whether glucose deficiency is a factor in producing symptoms in a given patient should be arrived at through one or more

of the following four different lines of evidence: (1) the history, (2) the glucose tolerance test, (3) the response to insulin, and (4) the effect of dietary treatment.* Each of these diagnostic methods will now be considered in more detail.

1. *The History.*—This is most important because it first suggests the possibility of relative hypoglycemia, and unless taken carefully the condition will usually be overlooked. *Whenever a patient has symptoms referable to the cardiovascular system which recur frequently, but which have never at any time appeared within one hour after an ordinary meal, glucose deficiency should be suspected.* Every patient with recurrent attacks of any kind should be asked the direct question whether the attacks bear any relation to meals. Frequently, the patient, thinking the physician is trying to find out whether the seizures are induced by meals, will answer in the negative. One should then proceed further to ask the patient if he can specifically recall any attack which has occurred shortly after a meal. If the patient is certain that an attack has occurred within one hour after the end of a meal, relative hypoglycemia can probably be excluded, at least as the sole factor, but it cannot be excluded as one of several precipitating factors. If the patient has had numerous seizures and none of these have occurred within two hours after meals it is probable that sugar deficiency may be playing a role.† Some patients have themselves noted that eating tended to relieve their symptoms. However, other patients, because they were afraid to eat during a self-diagnosed "heart attack," do not know whether food affects the symptoms.

2. *Blood Sugar Curves.*—This is a helpful diagnostic procedure but has certain limitations. It should be remembered that one person may have a blood sugar of 40 mg. per 100 c.c. without symptoms, and another person may have definite symptoms of glucose deficiency with a blood sugar of 65 to 70 mg. When one recalls that patients with diabetes may have symptoms from insulin overdosage with a blood sugar at or above the normal value, one realizes that the glucose level is not an absolute diagnostic criterion. Of the thirty-one cases with which this paper deals, and in which the diagnosis of relative hypoglycemia has been made, a glucose tolerance test was carried out in twenty-eight. The patients were given glucose orally—approximately 1 Gm. per kilogram of body weight—and specimens of venous blood were taken at intervals thereafter. Blood sugar was measured according to the Folin-Wu technique. The results may be analyzed as follows:

*A fifth method of study—measurement of the blood sugar level when the symptoms are present—can rarely be carried out because the physician does not usually have the opportunity to see the patient at this time.

†We do not mean to imply that all symptoms which appear more than two hours after meals are of hypoglycemic origin. Such is certainly not the case. There is, for example, no reason to assume that the hunger pain of duodenal ulcer is related to a low blood sugar. Furthermore, we have observed a few instances in which symptoms related to the cardiovascular system appeared quite regularly three to five hours after meals and were relieved by eating, but in which careful studies showed clearly that the seizures were not related to the carbohydrate metabolism. It is probable that, in certain patients with cardiovascular disease, hunger contractions of the stomach may induce symptoms, through reflex effects on the heart or blood vessels.

The *fasting* values for the blood sugar varied between 67 and 121 mg. per 100 c.c.; they were less than 80 in only three instances and more than 100 in only one case. Obviously, measurement of the fasting sugar level is of little or no value in detecting cases in which this disorder is mild.

Wide variations were encountered among the different patients with regard to the highest and lowest values at the various times after the administration of glucose. The lowest blood sugar values were observed at three hours in eighteen instances, at two hours in six cases, and at four hours in four patients. Since in all instances the minimum levels were obtained two to four hours after the administration of glucose, it is evident that insofar as the diagnosis of relative hypoglycemia is concerned, there is no need to take blood samples at one-half, one, and five hours after the sugar has been ingested, although this may be desirable for interpreting the results as regards etiology.

The *lowest* level of blood sugar during the glucose tolerance test varied considerably in different patients. Values of less than 50 mg. per 100 c.c. were observed twice; other minimum levels were: 50 to 59, seven cases; 60 to 69, eleven patients; 70 to 79, seven instances; more than 80, once. No correlation was found between the severity of the symptoms during the spontaneous seizures and the minimum blood sugar value observed in the curves. Thus, one patient became unconscious after a severe attack of pain in the chest, and while in this condition had a blood sugar value of 35 mg. per 100 c.c. He recovered rapidly after the intravenous administration of glucose. However, several days later, when the sugar tolerance curve was measured, the lowest value found was 79 mg. per 100 c.c. of blood. Observations such as this indicate clearly that curves of blood sugar are of limited value in the diagnosis of mild relative hypoglycemia. (Such a statement obviously applies only to sugar curves as usually measured. It is probable that the use of a standard preparatory diet, as recently advocated by Conn,[2] would have made our data more significant.)

The *shape* of the blood sugar curves was likewise very variable. Four patients showed flat curves, with less than the normal rise and a normal or slightly exaggerated decline. Twelve subjects exhibited a normal rise, followed by an abnormally great diminution. Eight patients displayed an unusually large increase in blood sugar, and in five of these the subsequent decline was striking, whereas in the other three instances the rate of decline was greater than normal but the actual level reached was not less than that of healthy persons. Four patients had curves which seemed to be normal in all respects. Curves of these several types are illustrated in Fig. 1.

The data obtained by measuring the blood sugar of these patients are by no means convincing. Although most of the patients did at times have values somewhat lower than those usually found in healthy persons

of the same age and dietary habits, the differences were not striking. We have frequently observed patients who were entirely free of symptoms at times when their blood sugar values were just as low as the lowest level found in many of these patients. Apparently, different persons display marked variations in their sensitivity to hypoglycemia.

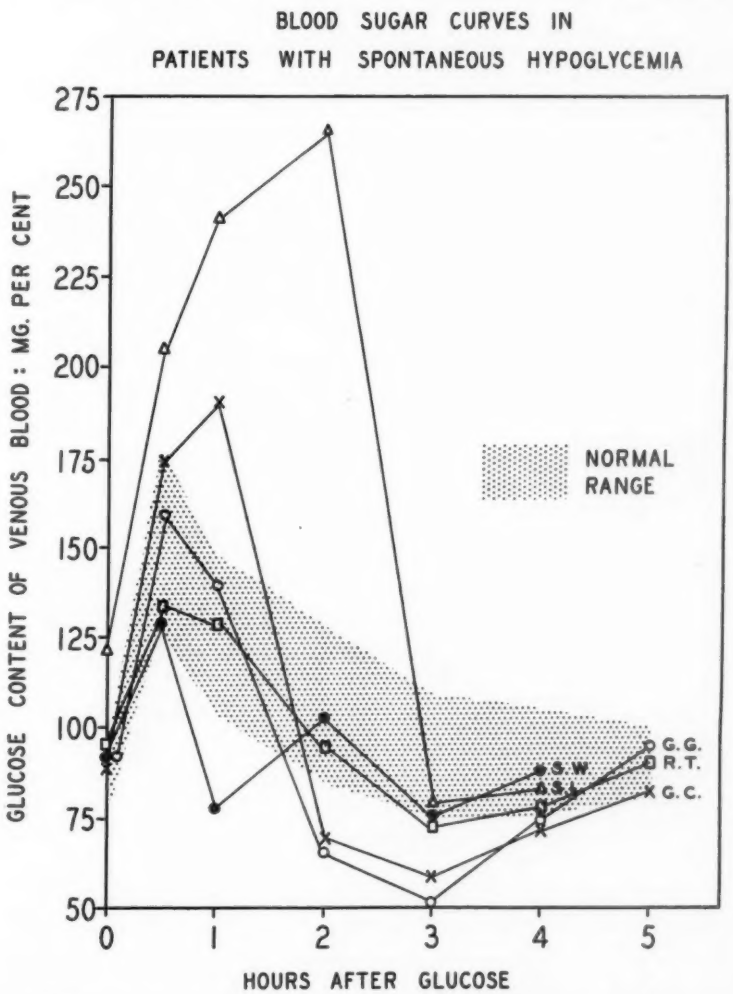

Fig. 1.—Different types of blood sugar curves encountered in patients with symptoms of glucose deficiency are illustrated. At the time the observations were made the patients were free of symptoms. It is probable that the blood sugar curves would have been more significant if the patients had been placed on a standardized diet for several days prior to the studies.

We have gained the impression that the rate of decline in blood sugar may be just as important as the minimal level. Furthermore, it is well known that age and previous dietary habits have a marked influence on the glucose tolerance. Because of these several facts we believe that the measurement of blood sugar often is less useful than other procedures

in determining whether glucose deficiency is a factor in the production of symptoms in a given patient.*

3. *The response to insulin* was not investigated in the earlier cases, but later was studied routinely, and was found to be of considerable value in diagnosis. Ten units of insulin were injected three to four hours after a low-protein meal. If at the end of an hour no symptoms appeared, a second injection of 15 units was given. If after an additional ninety minutes no complaints developed, the patient was usually given his meal and the procedure resumed on the following day, employing larger doses. Since discomfort can be induced in almost anyone by sufficient dosage of insulin, the important point in the test is not whether symptoms occur, but whether the symptoms induced by insulin are the same as those which occur spontaneously. At the beginning of this study it was our custom to take blood for analysis of sugar content at the time symptoms developed. Because of the marked variation in the sensitivity of different persons to hypoglycemia, this procedure has been found to be of relatively little value, and we now rely almost entirely on the patient's statement as regards his subjective sensations. Obviously, care must be exercised in interpreting the subjective reaction of psychoneurotic persons. However, as a rule, the patient's statement about his sensations, and their similarity or dissimilarity to the symptoms which brought him to the physician, proved to be accurate. If there was any doubt the procedure was repeated, using injections of saline or atropine. In this way the factors of malingering and suggestion can be controlled. The insulin response test should not be used on patients who have severe or dangerous manifestations during their seizures. We have used it only rarely on people with angina pectoris or hypertensive encephalopathy.

In interpreting the subjective reactions to the procedure it is important to remember that the induced symptoms may differ from those which occur spontaneously, because fright is likely to be less marked when the symptoms are induced in a hospital or in a physician's office than when they occur spontaneously in a less reassuring environment. Furthermore, a patient may have cardiovascular symptoms of more than one type and due to more than one cause, whereas the administration of insulin induces only those symptoms which are precipitated by glucose deficiency. We have, on several occasions, observed women who had both menopausal and hypoglycemic symptoms. In such instances the patient may state that the "spells" were not reproduced by the injection because she is looking for an attack of "hot flashes," when actually the insulin did reproduce the weakness and palpitation which were among the presenting complaints.

Subject to the qualifications mentioned, the study of the response to insulin has proved to be of considerable value in the diagnosis of

*It is probable that our blood sugar curves would have been more significant if we had adopted a standard preparatory diet, as advocated by Conn.[2]

glucose deficiency as a factor in causing symptoms. This test has been carried out with negative results on numerous patients who subsequently proved to have no evidence—as ascertained by other procedures—of glucose deficiency. The response to insulin was studied in eighteen of the thirty-one cases included in this report. The test was inconclusive in three cases, but in the remaining fifteen a positive response occurred, i. e., some or all of the symptoms which brought the patient to the physician were reproduced by the administration of insulin. As a rule the patients were quite positive in their statements as to whether the induced symptoms were identical with their spontaneous symptoms, and in most instances further studies showed that their impressions were accurate.

As the result of our experience to date, we are inclined to regard the response to insulin, when properly controlled, as a valuable addition to the glucose tolerance test in the detection of relative hypoglycemia. Both methods, the one subjective and the other objective, have value and limitations.

4. *The Response to Treatment.*—In every case in the series a low-carbohydrate, high-protein diet was prescribed. Since most of the subjects lived in other cities, adequate "follow-up" data are available on only fifteen of the thirty-one patients, and marked improvement has apparently occurred in thirteen of these.* In two instances no benefit was observed from the dietary regime. We suspect that the diagnosis of relative hyperinsulinism was incorrect in these two cases, but, since the suspicion is unproved, they are included in the series. We therefore now regard the response to treatment as one of the most useful means of diagnosis. The reasons why the high-protein diet is employed, and further considerations with regard to the therapy of relative hypoglycemia will be considered later in this communication.

GENERAL CLINICAL PICTURE OF PATIENTS WITH RELATIVE HYPOGLYCEMIA

Most of the studies which have dealt with spontaneous hypoglycemia have been concerned with the severe manifestations. Such patients have usually displayed evidence of gross disturbance of the function of the pancreas (benign or malignant neoplasm, or diffuse hyperplasia), liver, pituitary, adrenals, or kidneys (renal glycosuria). However, the patients dealt with in the present report, which includes much milder instances of glucose deficiency, were quite free of evidence of any gross dysfunction of these organs. Most of them gave a story of utilizing a diet rich in starches, but in some instances no such history could be obtained.

*Obviously, only those symptoms caused by hypoglycemia have been relieved, and in many of the cases these manifestations have been the less important ones. Thus, in cases of angina pectoris the attacks which come on at rest, three to four hours after meals, may be relieved, and the seizures appearing with exertion remain unaffected.

Of the thirty-one patients, twenty were men. The oldest subject was 65 years of age, the youngest, 26 years. Most of the patients were between the ages of 35 and 55 years.

The complaints during the attacks were quite variable; the most common were nervousness (twenty-five patients), weakness (twenty-three instances), palpitation (seventeen cases), and pain in the chest (fifteen cases). In nine cases the pain complained of did not resemble angina pectoris; it consisted of vague precordial discomfort or aching (six cases), a stabbing sensation (two patients), or a feeling of pressure relieved by belching (one instance). However, there were six patients—discussed in more detail later—who had pain which closely resembled that of angina pectoris. Thirteen of the patients confessed to a considerable degree of fright and anxiety during their attacks, and it is probable that some of the other patients experienced this symptom but were reluctant to admit it. Nine persons mentioned dizziness as a prominent feature of the attacks. Eight subjects complained of dyspnea, which usually consisted of repeated sighing and inability to "get a deep breath," rather than the panting and labored breathing commonly associated with structural cardiac disease. (Although we have seen four patients with cardiac asthma who obtained marked relief from taking food during the attacks, in none of them could the seizures of dyspnea be induced by insulin.)

Among the less common symptoms were "choking in the throat," which occurred in three cases and was indistinguishable from the globus hystericus, arrhythmias (seven patients), focal paresthesias (two patients), headache (three patients), "sinking feeling" (three patients), and blurring of vision (two patients). The role of glucose deficiency in precipitating certain arrhythmias, in inducing attacks of hypertensive encephalopathy, and in relation to carotid sinus syncope will be discussed later.

When observed during the attacks the patients usually appear anxious, the heart beat is forceful, and the heart sounds are loud; the pulse volume is full in most instances, but diminished in others. The pulsations of the aorta are usually pronounced in the suprasternal notch, and the peripheral pulsations are prominent. Tachycardia is the rule, but occasionally bradycardia occurs. The blood pressure may vary in either direction, but an increase in pulse pressure is the most common change. The skin is sometimes flushed and sometimes pale. Frequently, the physician does not have the opportunity to observe the patient during the attacks, and, when the examination is made during a period of freedom from complaints, objective abnormalities are usually not found.

The most important *associated disorders* in this series of patients have been as follows: hypertension (nine cases), cardiac neurosis (seven instances), hypothyroidism (six instances), arteriosclerotic heart disease (four patients), menopausal syndrome (four cases), paroxysmal tachy-

cardia (three cases), hypertensive encephalopathy, rheumatic heart disease, and hypersensitive carotid sinus (two cases each), and paroxysmal auricular fibrillation (one case).

RELATIVE HYPOGLYCEMIA IN RELATION TO CARDIAC NEUROSIS

The reader will, no doubt, already have noted the similarity of this clinical picture to that displayed by certain patients with cardiac neurosis. The two conditions may present practically identical features, both subjective and objective. Fourteen of our thirty-one patients were considered at first to be suffering from cardiac neurosis because they presented a multiplicity of complaints associated with a paucity of objective abnormalities. After more careful study we were convinced that seven of these patients were not neurotic at all, for all of their troubles could be accounted for by glucose deficiency. However, the conditions were more complex in the other seven patients of this group. Even after the abnormality in glucose metabolism had been recognized, these patients displayed other features which still warranted the diagnosis of cardiac neurosis. In most of them it was thought that the neurosis had resulted from the mental stress brought about by fear of heart disease because of symptoms which were originally induced by the relative hypoglycemia, but which the patient ascribed to "heart trouble." Even in such cases the correction of the glucose deficiency by proper dietary measures resulted in marked relief of the neurotic symptoms, because one of the chief causes of fear had been removed.

One patient, who was diagnosed as having both relative hypoglycemia and cardiac neurosis, merits especial comment because of certain unusual features. This 49-year-old business man complained of palpitation, weakness, choking in the throat, and fullness in the head. These symptoms appeared only when he became engaged in a business argument. He thought that he had cardiac disease, but had consulted several physicians, all of whom had told him that his heart was normal and that his trouble was due to "nerves." On careful questioning it was found that his important business conferences were commonly held about two or three hours after his breakfast, which consisted almost entirely of carbohydrates. The heart was objectively normal to all of the ordinary methods of examination. The glucose tolerance test (Fig. 1, patient G. C.) displayed a high peak (190 mg. per 100 c.c. at one hour, followed by a sharp decline to 58 mg. at three hours. The injection of insulin—15 units—produced a typical attack. His seizures could be prevented by having his business conference held one hour after a protein-rich breakfast rather than three hours after a high-carbohydrate meal. Marked improvement has persisted for nearly two years since his dietary habits were changed. However, he still has some heart consciousness and is still fearful of heart disease. The observation that in this patient the combination of mental stress and hypoglycemia was apparently necessary in order to produce the complaints suggests that the symptoms may have been related to release of adrenalin. However, this suspicion remains unproved.

Four of the fourteen patients who experienced symptoms resembling those of cardiac neurosis were also suffering from the menopausal syndrome. It was difficult to disentangle the symptoms of the latter condition from those of relative hyperinsulinism, for both conditions

are common causes of palpitation, tachycardia, and other functional disturbances of the circulation. In none of these patients did the injection of insulin induce "hot flashes," and this symptom was not relieved by dietary regulation. In these four patients benefit occurred both from estrogenic therapy and from control of diet. Neither procedure alone was as helpful as the two together. Our data do not justify any conclusions as to the frequency of glucose deficiency as a factor in the production of some of the cardiovascular symptoms commonly observed in women during the menopause.

The similarity between the clinical manifestations associated with a decline in blood sugar and the phenomena of true cardiac neurosis is so great that we are no longer willing to make a dogmatic diagnosis of cardiac neurosis without excluding spontaneous hypoglycemia.

RELATIVE HYPOGLYCEMIA AS A FACTOR IN PRECIPITATING CERTAIN CARDIOVASCULAR SYNDROMES

Many cardiovascular disorders are associated with recurrent attacks of the particular symptom which is troublesome to the patient, and the seizures are usually separated by intervals of comfort. Such attacks are of the most varied types, and, among the factors which may precipitate them, a decline in blood sugar plays an important role. Some of the conditions which can in certain cases be induced by relative glucose deficiency are the following:

1. *Disturbances of Cardiac Rhythm.*—We have seen three patients with paroxysmal auricular tachycardia whose attacks tended to occur two or more hours after meals; regulation of their diet was followed by a diminution in the frequency of the attacks. We do not mean to state that a low blood sugar is a factor in inducing attacks of paroxysmal tachycardia in all patients, or in inducing all of the attacks in any patient. Such is not the case. Several patients with recurrent attacks of paroxysmal tachycardia have been carefully studied for evidence of hypoglycemia with entirely negative results. However, there are certain cases of this disorder in which a low blood sugar may be one of several precipitating factors; the others are abdominal distention, emotional upsets, unusual muscular effort, the ingestion of iced drinks, fatigue, or, in many instances, are unknown.

Paroxysmal auricular fibrillation has not in our experience been commonly associated with a low blood sugar. However, this association seemed to be definite in one instance.

Of the thirty-one patients included in this study, three complained of "skips" of the heart as a troublesome feature of the attacks. In each of these cases ventricular extrasystoles were induced by insulin, and their frequency was much reduced after a high-protein diet had been instituted. Obviously, we do not regard glucose deficiency as the usual cause of premature beats, but in an occasional case the decline in blood sugar seems to be an important exciting factor.

2. *Angina Pectoris.*—The relationship of glucose deficiency to angina pectoris is somewhat complex, and will be discussed in more detail later. Here we shall be satisfied with pointing out that attacks of angina pectoris which occur at rest, with no apparent cause, are sometimes due to spontaneous hypoglycemia. Such seemed to be the case in six patients in this series.

3. *Hypertensive Encephalopathy.*—In two instances the relationship between recurrent attacks of hypertensive encephalopathy and relative glucose deficiency seems to have been established. We suspect that such a relationship existed in two other patients, but their condition was so serious that investigation of the response to insulin seemed unjustifiable. Since treatment by diet caused the attacks to become less frequent but did not result in their complete cessation, it seems clear that relative hypoglycemia was only one of several precipitating factors in these cases, and, in our experience, it plays no role at all in the majority of cases of hypertensive encephalopathy.

4. *Hypersensitivity of the Carotid Sinus.*—Two patients were observed who had spontaneous attacks of syncope; their seizures could be readily reproduced by pressure on the carotid sinus, but only provided such pressure was applied three to four hours after meals. Apparently, the sensitivity to stimulation of the carotid sinus may, in certain cases, be increased by relative glucose deficiency.

5. *Paroxysmal Dyspnea.*—Four patients were observed with left ventricular failure and paroxysmal attacks of shortness of breath; they said that the attacks appeared only on an empty stomach and were relieved by eating. One of these patients was not studied carefully, and the relationship of his attacks to hypoglycemia remains uncertain. The other three patients were thoroughly investigated, and, even though the relief of dyspnea by taking a small amount of food was striking, it was found that the attacks bore no relation to a low blood sugar. The blood sugar during the attacks was normal. The administration of insulin induced weakness, sweating, and palpitation, but no dyspnea. Furthermore, it was found that when the attacks began, relief would come within one minute after the ingestion of food, or even after a cup of coffee only. Two of these patients were given trials with high-protein diets but obtained no benefit. Apparently in these cases some reflex factor, possibly hunger contractions from the stomach, was responsible for the relationship of the attacks to lack of food. (It is possible that patients of this type are fairly common, and that some of the cases in the literature of supposed "hyperinsulinism" represent various reflex disturbances. Furthermore, we have seen one patient who had symptoms suggestive of hypoglycemia, but who appeared on further study to have reflex cardiac acceleration as the result of the pain of duodenal ulcer.)

These four patients with cardiac asthma are, of course, not included in the series because their symptoms were not caused by a decline in

blood sugar. However, there were eight patients with hypoglycemia who had the sighing breathing, associated with a feeling of inability to take in enough air, which is so commonly seen in neurotic subjects. Furthermore, we have recently observed a patient who had typical hysterical hyperpnea which resulted in tetany; her hyperpnea occurred only when she became frightened as the result of palpitation and premature beats induced by glucose deficiency.

THE RELATIONSHIP OF RELATIVE HYPERINSULINISM TO ANGINA PECTORIS

It is not uncommon for patients who have typical angina of effort, not related to the blood sugar level, to have occasional attacks of discomfort at rest and without obvious cause. That such attacks may be induced by an unusually large meal, by emotion, or by temporary disturbances of the cardiac rhythm is well known. It is also known that hypoglycemia *induced* by insulin may cause anginal attacks in diabetic patients with coronary disease. However, Sippe and Bostock[3] have pointed out that *spontaneous* hypoglycemia may precipitate attacks of angina pectoris, and in our experience this is one of the most important causes of mild anginal attacks at rest, in the absence of an obvious precipitating factor. Whenever a patient has unexplained attacks of angina pectoris at rest, relative hypoglycemia should be suspected, and, it found, appropriate treatment instituted.

Spontaneous hypoglycemia and angina pectoris may be related in another way, i. e., the lowering of the blood sugar may induce an attack of paroxysmal tachycardia or of paroxysmal auricular fibrillation which in turn may lead to an attack of angina pectoris.

In the instances which have been mentioned, there already is some cardiac disturbance which can be precipitated by a low blood sugar. However, in rare instances, typical attacks of angina pectoris may occur as the result of hypoglycemia in patients who have no other demonstrable cardiac abnormality. This remarkable sequence of events was observed in a 27-year-old white woman who complained of recurrent attacks of constrictive pain radiating from the substernal and precordial region to the left shoulder, the left arm, and the ring and little fingers of the left hand. The attacks were not caused by muscular effort, and she was able to engage in athletics without symptoms. Although she had had numerous seizures, she could not recall any which had appeared within ninety minutes after a meal. The heart was entirely negative to physical examination, and no abnormalities were revealed by either electrocardiographic or fluoroscopic methods. Her glucose tolerance curve was abnormally "flat" (patient S. W., Fig. 1). The attacks could be induced by insulin, and the pain was relieved by either nitroglycerin or orange juice. During such an attack, elevation of the S-T segments in the electrocardiogram was noted. The use of a high-protein, low-carbohydrate diet, with intermediate feedings, was followed by marked relief.

The occurrence of anginal attacks without relation to effort in this case might be cited as evidence against the idea, first expressed by Keefer and Resnik,[4] and now widely accepted, that angina pectoris is dependent on myocardial anoxia. However, since insulin causes an increase in the cardiac output,[5] and hence in the cardiac work, and,

further, since one would expect deficiency of fuel to have the same general effect as deficiency of oxygen, the occurrence of angina during glucose deficiency in a patient with no structural lesion capable of producing anoxia cannot be considered as evidence against this well-established concept.

THE RELATION OF THE SYMPTOMS OF GLUCOSE DEFICIENCY TO THE APPARENT BLOOD SUGAR LEVEL

Although the idea that a direct quantitative relationship exists between the severity of the symptoms of glucose deficiency and the level of the blood sugar, as ordinarily measured, seems to be widely accepted, there is convincing evidence that such is not the case. It should be remembered that the usual methods for estimating blood sugar are not specific, but measure instead a number of substances which reduce copper sulphate. Patients with diabetes may have symptoms of hypoglycemia with apparent values for blood sugar which are well within the normal range. Likewise, a patient may be without symptoms when the blood sugar is markedly reduced, and, at other times, have severe hypoglycemic reactions with similar sugar levels. Such an instance has recently been reported by Conn and Conn.[6]

In order to obtain further data on this question, we have made a number of observations on persons with symptoms of glucose deficiency, either spontaneous, or induced by insulin. The following protocols are illustrative.

Subject M. T., a woman, 42 years old, frequently had weakness, dizziness, blurring of vision, and palpitation three hours after meals which were relieved by eating. The blood sugar one hour after a light carbohydrate meal was 159 mg. per 100 c.c. Two hours later, when the typical symptoms appeared, her blood sugar was 80. The ingestion of 25 Gm. of glucose produced relief in ten minutes, and raised the blood sugar to 100. These observations were repeated on two other occasions, and values of 64 and 73 were found during the symptoms. On another date she was given 20 units of insulin, and the symptoms were marked when her blood sugar reached 56. It subsequently fell to 27, with no increase in symptoms except for the appearance of sweating and hunger. Twenty minutes after eating a bar of candy the blood sugar was 50, but all symptoms were relieved.

Subject M. M., a 38-year-old man, had mild attacks of palpitation, sweating, and weakness two to four hours after carbohydrate-rich meals which were relieved by eating. During such an attack his blood sugar was 62. He was given 20 units of insulin and his symptoms became intensified; the blood sugar was 38. Within a few minutes after the ingestion of 25 Gm. of glucose he was relieved, but the blood sugar was 41.

Subject T. H., a man, aged 41 years, had no manifestations of spontaneous hypoglycemia. Three hours after a meal his blood sugar was 82. Forty-five minutes after receiving 20 units of insulin his blood sugar was 26. He had no symptoms other than slight dizziness and a feeling of warmth in the abdomen. Twenty minutes later he had blurring of vision, marked hunger, and profuse sweating, and the blood sugar was 32. Fifteen minutes after eating two candy bars his blood sugar was 47 and the symptoms had disappeared.

These observations indicate that: (1) Certain persons may have symptoms of glucose deficiency when the blood sugar is normal. (2) Other persons may have extremely low values for blood sugar with minimal symptoms. (3) Relief of symptoms may occur with only a slight increase in blood sugar. (4) In a given patient there is very little parallelism between the level of blood sugar and the severity of symptoms. (5) Symptoms of glucose deficiency are more likely to be related to the rate of decline than to the absolute level of blood sugar. (6) Glucose deficiency, when induced by insulin, is likely to be associated with lower levels of blood sugar than when it occurs spontaneously.

THE MANAGEMENT OF RELATIVE HYPOGLYCEMIA

Of the several different plans we have tried in various cases, the most generally satisfactory has been the low-carbohydrate, high-protein diet suggested by Conn, et al.[7] The three regular meals are relatively small, and are supplemented by intermediate feedings; the total caloric intake is sufficient to maintain the weight of thin patients, or can be adjusted to cause a slow loss of weight in obese patients. High-carbohydrate diets with frequent feedings have not usually caused improvement. Apparently the marked rise in blood sugar produced by such feedings leads to excessive insulin production. Diets low in carbohydrate and abundant in fat have been beneficial, but apparently less so than the high-protein diet. Newburgh and Conn showed that, after a protein meal, the blood sugar curve is relatively stable, and free of the postprandial decline which commonly occurs after a carbohydrate meal; this is because the protein is converted into amino acids which, in turn, are changed into glucose.

DISCUSSION

Although relatively little has been written about *spontaneous* hypoglycemia in relation to the vascular system, a few isolated reports have appeared. Most of these have been summarized by Harris,[8] who cites tachycardia, bradycardia, palpitation, extrasystoles, sense of suffocation, and precordial pain as some of the manifestations which may occur. Waters[9] reported a patient with paroxysmal tachycardia whose attacks were precipitated by glucose deficiency. Sippe and Bostock[3] emphasized the importance of spontaneous hypoglycemia in the production of angina pectoris.

The circulatory manifestations of *induced* hypoglycemia have been studied by a number of authors. The prominent arterial pulsations mentioned by Wiechmann and Koch[10] and Messinger [11] appear to be related to the increase in cardiac output which was demonstrated by Lauter and Baumann,[12] and by Ernstene and Altschule.[5] Messinger,[11] studying patients with schizophrenia who were treated by insulin shock, mentions flushing, pallor, increased pulse pressure, bounding pulse,

"pistol-shot" sounds over the arteries, capillary pulsations, and even transitory to-and-fro murmurs along the left sternal border. With the exception of the diastolic murmur, these phenomena are those which we have commonly observed in our patients with glucose deficiency. The signs, in general, are similar to those seen in patients with thyrotoxicosis or, for that matter, in normal persons immediately after exercise. These typical manifestations of the overactive heart are, as has been pointed out elsewhere,[13] the usual signs of an increase in cardiac output. During hypoglycemic states there are at least two factors which may cause an increase in cardiac output. One of these is the release of epinephrine, and the other is an effect similar to that of anoxia, for it seems obvious that fuel deficiency will tend to produce in the tissues metabolic disturbances similar to those induced by oxygen deficiency. Whether the circulatory manifestations of hypoglycemia are entirely the result of epinephrine release, are dependent on dilatation of peripheral blood vessels as the result of fuel deficiency, or are related to other and unknown factors is uncertain. Since both anoxia and epinephrine cause similar clinical evidences of circulatory overactivity, and since both cause an increase in cardiac output,[14, 15] it is probable that each mechanism may play a role in producing the hemodynamic changes accompanying hypoglycemia.

Throughout this communication we have used the terms "relative hypoglycemia" and "glucose deficiency" to designate, respectively, the syndrome and the metabolic disorder under discussion. These terms are not beyond criticism. The fact that administration of sugar relieves certain symptoms does not prove beyond question that lack of sugar is the essential factor in their production. It is possible that, in certain patients, and especially those who have symptoms with apparently normal values for blood sugar, the primary disturbance may be in some of the enzymes or hormones which are concerned in the complex processes of transfer, storage, release, and combustion of carbohydrate. The balance of these factors may be so disturbed that in certain persons a normal carbohydrate metabolism can be maintained only in the presence of a high "sugar pressure" in the tissue fluids. Until more is known concerning the disorders of the intimate processes of glucose metabolism it seems justifiable to use the term "relative hypoglycemia," even though it is recognized that the glucose deficiency is a result, and not a cause, of the unknown primary disorder. Meanwhile, the realization that measurements of blood sugar have only limited value in the detection of these common and mild disorders of carbohydrate metabolism should lead to the more widespread use of the diagnostic methods which have been discussed. The recognition of these disorders is particularly important because they commonly produce anxiety, through fear of heart disease, out of all proportion to the discomfort, and because they can usually be satisfactorily treated by regulation of the diet.

SUMMARY

Disturbed carbohydrate metabolism may precipitate various manifestations referable to the cardiovascular system. These manifestations can be recognized by their appearance two or more hours after meals, their relief by the ingestion of glucose, and their reproducibility by administering insulin. When the symptoms are present, the blood sugar level is usually within the lower limits of normal, or only slightly subnormal. The disturbance of carbohydrate metabolism which is responsible for these symptoms has, for want of a better term, been designated as "relative hypoglycemia."

Relative hypoglycemia is a common factor in the production of symptoms referable to the circulatory system, and has been found in thirty-one of the last two hundred four of our patients with cardiovascular complaints.

Relative hypoglycemia may produce subjective and objective manifestations identical with those commonly observed in patients with cardiac neurosis. The two conditions can be differentiated only after the most thorough study, and they frequently coexist.

Relative hypoglycemia may be a "trigger" factor in precipitating various arrhythmias (including paroxysmal tachycardia), as well as attacks of angina pectoris, hypertensive encephalopathy, carotid sinus syncope, and circulatory disturbances associated with the menopause.

Relative hypoglycemia frequently is associated with pain in the chest which is nonanginal in character. Occasionally it induces, in patients with typical effort angina, attacks of angina pectoris at rest. Rarely patients without any evidence of structural cardiac disease may have, as the result of glucose deficiency, attacks of severe pain which are identical with seizures of angina pectoris in all respects except for the absence of a relation to muscular effort.

The circulatory manifestations of relative hypoglycemia are the same as those observed after the experimental or therapeutic administration of insulin. They appear to be related to two mechanisms: release of epinephrine, and alterations comparable to those which occur in anoxia. The increased venous return, so brought about, causes an augmented cardiac output and the typical signs of the "overactive heart."

The diagnosis of the milder instances of relative hypoglycemia has been discussed, and it is concluded that the attempt to reproduce the symptoms in a given case by insulin administration is, in certain patients, a more valuable method than the glucose tolerance test. Both methods are less important than the history.

When relative hypoglycemia is causing symptoms, marked benefit can usually be obtained by the use of a diet which is poor in carbohydrates and rich in protein, with intermediate feedings. Observation of the response to such a diet is therefore at times a helpful diagnostic measure.

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THE EFFECT ON MAN OF POTASSIUM ADMINISTRATION IN RELATION TO DIGITALIS GLYCOSIDES, WITH SPECIAL REFERENCE TO BLOOD SERUM POTASSIUM, THE ELECTROCARDIOGRAM, AND ECTOPIC BEATS

JOHN J. SAMPSON, M.D., EDMOND C. ALBERTON, M.D., AND BENJAMIN KONDO, M.D., SAN FRANCISCO, CALIF.

SAMPSON and Anderson,[1] in 1930 and 1932,[2] demonstrated that approximately 50 per cent of ectopic heart beats in persons with otherwise normal hearts or with various types of heart disease could be abolished by the oral administration of different potassium salts in doses varying from 1 to 15 Gm. In this series there was one patient who had auricular fibrillation and bigeminy; the ventricular ectopic beats were produced by digitalis intoxication. These ectopic beats disappeared after the administration of 3 Gm. of potassium chloride.

It was believed that the changes in the physicochemical state of the heart muscle which tend to produce ectopic beats probably have different origins, for the ectopic beats were abolished in only 50 per cent of the cases in which potassium was used.

In view of the work that has been done on the effect of digitalis on blood serum potassium and the potassium content of heart muscle, the single case of digitalis intoxication in this series suggested that there may be a correlation between the disturbing effect of digitalis on the potassium balance of the heart muscle and its counteraction by potassium administration. If this effect of digitalis were a constant cause of ectopic beats, potassium administration should uniformly abolish them. It was therefore considered important to make a further study of digitalis therapy and digitalis intoxication in the light of the possible effects of potassium administration on the potassium content of the blood serum and on ectopic beats.

The theory that an alteration of the calcium-potassium ratio in the heart muscle in favor of calcium can explain the action of digitalis has been advanced by several investigators, notably Cattell and Goodell.[3] The experimental observations in support of this theory are (1) that an excess of calcium increases the force of myocardial contraction, and potassium tends to relax the myocardium;[4-8] (2) that the addition of calcium increases the tendency toward ectopic beat formation,[9] whereas potassium generally diminishes it;[3, 10-13] and (3) that the T waves of the electrocardiogram tend to be elevated by potassium[3, 14-16] and depressed by calcium.[21-24] (The T waves may be either elevated or de-

From the Department of Medicine, University of California Medical School, the Harold Brunn Cardiovascular Laboratory of the Mount Zion Hospital, and the Laguna Honda Home of the Department of Public Health, San Francisco.

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pressed by potassium, as shown in cats by Chamberlain, et al.,[17] and in man by Bamber[19] and Stewart and Smith.[20])

Likewise it has been demonstrated (1) that digitalis is ineffective unless at least a small amount of calcium is present in the perfusate of heart muscle;[25, 26] (2) that serious and occasionally fatal synergism occurs when calcium salts are injected into patients under digitalis therapy,[27, 28] although Winkler, et al.,[16] could not demonstrate synergistic effects of digitalis and calcium in dogs; (3) that digitalis and strophanthin cause loss of potassium from the heart muscle;[4, 30-32] and (4) that strophanthin sensitizes the heart to acetylcholine and to high vagal tone,[33, 34] which two factors, in turn, are reported to be associated with potassium accumulation in muscle tissue and probably to potassium release from muscle cells.[35]

Although these data seem to support the "calcium" theory of digitalis action, contradictory evidence has been assembled. Wedd,[37] Hagen,[38] and Boyer and Poindexter[39] demonstrated an increase in the potassium content of the myocardium when digitalis glycosides were used in therapeutic doses. These observations were adapted by the latter investigators to the conception that the functional integrity of the muscle cell is partially dependent on its potassium content, and that digitalis partially prevents the loss of potassium from the myocardium when the heart is hypertrophied or damaged (Harrison, et al.,[40] Calhoun, et al.,[41] Wilkins and Cullen,[42] Mangun, Reichle, and Myers[43, 44]). A parallel has likewise been drawn between the lessening in the muscular weakness in Addison's disease after the deposition of potassium in muscle as a result of adrenal cortical hormone therapy, and this action of digitalis. It is of interest that there is a close chemical relation between desoxycorticosterone and digitoxigenin. The return of muscular power with the administration of potassium to patients with familial periodic paralysis (Stewart, et al.[45]) and Simmonds' Disease (Anderson[46]) also indicates the importance of proper potassium concentration in the maintenance of normal muscular function. In these diseases the T waves become elevated, indicating a cardiac, as well as a somatic, muscular effect. Thyrotoxicosis[47] also produces a loss of potassium from the muscle cell which is partially prevented by adrenal cortical hormone therapy.*[48] This may explain the increased dosage of digitalis necessary to affect a thyrotoxic patient with heart failure. The reverse of this action may hold true in myxedema.

In contrast to the disagreement on the effect of digitalis glycosides in therapeutic doses is the consensus of investigators that toxic doses of these substances uniformly cause a loss of potassium from somatic and cardiac muscle.[30, 37, 38] It would be expected that, if improvement in cases of myocardial efficiency is dependent on retention of potassium

*Current knowledge concerning potassium concentration in intracellular interstitial fluids and plasma in adrenal cortical insufficiency is not, we believe, in conflict with this work. An excellent summary of this subject is given by Kepler, E. J., and Wilson, D. M.: Diseases of the Adrenal Glands; Addison's Disease, Arch. Int. Med. 68: 979, 1941.

brought about by moderate doses of digitalis, toxic doses of digitalis, by causing potassium loss, would reduce the efficiency of the heart, but this is not the common clinical experience in cases in which moderate digitalis intoxication is indicated by nausea, visual symptoms, and ectopic heart beats.[49] It must, however, be recognized that digitalis in therapeutic doses occasionally abolishes ectopic beats, and produces them in toxic doses. One might assume that this is due to the effect on the potassium content of the heart muscle, but even this assumption cannot be accepted in the light of the action of oral doses of potassium in a test case (Case 13). In this case ectopic beats were present before digitalis was administered, and they were not affected by potassium. They did, however, disappear when digitalis was given in therapeutic doses. When ectopic beats reappeared with digitalis intoxication, they were promptly abolished by a 5 Gm., oral dose of potassium. This case presents not only significant evidence that there are physicochemical differences in the origin of ectopic beats, but also that there is a specific relation of these beats to the change of the potassium content, or the potassium-calcium ration of the heart muscle, as affected specifically by potassium administration and digitalis therapy.

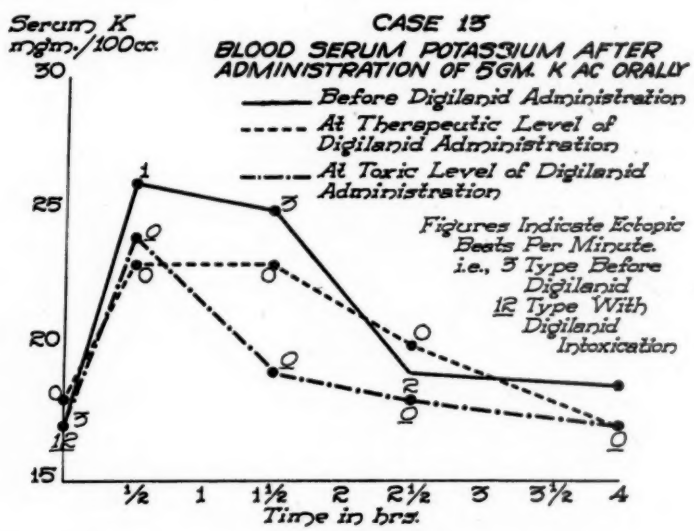


Fig. 1.

Since neither theory entirely fits the facts, no true explanation exists for the digitalis action on the calcium-potassium balance or for functional integrity of the myocardium. Simultaneous studies of the calcium as well as the potassium content of the heart muscle during digitalis therapy may uncover the determining factors.

The work presented in this paper is concerned largely with toxic doses of digitalis glycosides, and therefore only secondarily with the therapeutic effect of digitalis on the potassium or calcium-potassium balance in the myocardium. Thirty-three patients were studied; thirty-one, who

were more than 60 years of age, had arteriosclerosis, and two, aged 45 and 62 years respectively, had rheumatic heart disease. The pure lanatosides A, B, and C of digilanid were used chiefly in order to be sure of consistency and uniformity of action and that the doses administered were comparable in milligrams of active substance.[50] Digitalis leaf tablets were used orally in two instances, Cedilanid in one instance, and Digilanid (Sandoz), either initially or for at least two weeks after discontinuance of digitalis, in twenty-eight instances. All of this group were given large enough doses, as indicated in Table I, to produce constant nausea and marked slowing of the ventricular rate when auricular fibrillation was present. Thirteen, or slightly over one-third of these patients, developed ventricular ectopic beats. Whether this low incidence of ectopic beats was due to the particular lanatosides used or to failure of criteria of intoxication cannot be stated. The latter seems improbable because of the other evidences of toxicity.

In seventeen cases, studies were made of the blood serum potassium by the argenti-cobalt-nitrate method,[51] with final readings on the Evelyn colorimeter.[52] Table I illustrates eighteen cases in which potassium was given. In one of these, blood potassium studies were not done (Case 6). In most instances these were made when the patient was fasting, and at one-half hour, one and one-half hours, two and one-half hours, and four hours after the administration of 5 Gm. of potassium acetate orally in a 25 per cent aqueous solution. In three instances, 10 Gm. of potassium acetate were used. In three cases (Cases 9, 10, and 16) preliminary studies were made, but inasmuch as no ectopic beats were produced by toxic doses of digitalis, no potassium estimations were made after digitalis had been given.

Blood serum potassium estimations have been made by other investigators after the administration of potassium salts orally to human subjects.[3, 10, 14, 15, 53-55]

The curves obtained on our patients resemble those reported previously, except that the maximum rise of the potassium level occurred later in the previously reported cases. There was some variation in the time of the maximum rise of the blood serum potassium which was probably the result of differences in absorption. This maximum was reached in one-half hour in nine cases, and in one and one-half hours in five cases. In general, the potassium content of the blood serum was nearly identical one-half and one and one-half hours after potassium administration, and it fell practically to the fasting level within two and one-half to four hours. In one case (Case 12), the potassium content of the specimens at the one and one-half hour period was higher than at the one-half hour period, and, after digitalis therapy, the higher level was at the one-half hour period in one instance, and the levels were identical in one other instance.

As is best illustrated by Case 14, there was no essential difference in the blood serum potassium curve before digitalis was given and at the

later dates, when the patient had received digitalis in therapeutic or toxic doses.

Castleden[10] showed that ectopic beats could be abolished by the oral use of potassium after they had been produced by epinephrine and

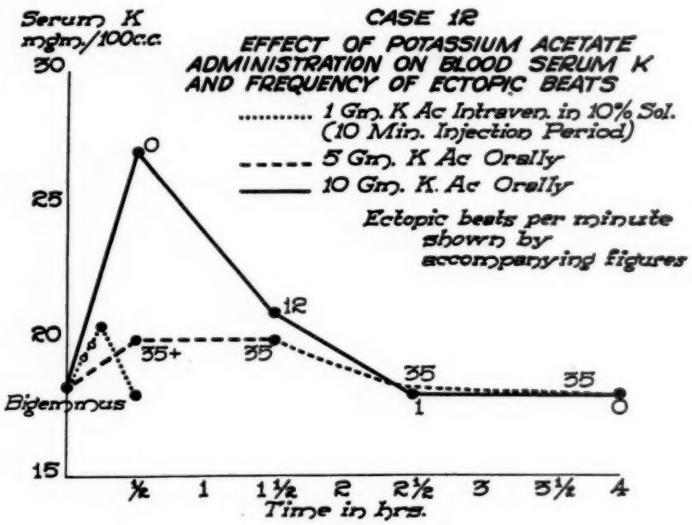


Fig. 2.

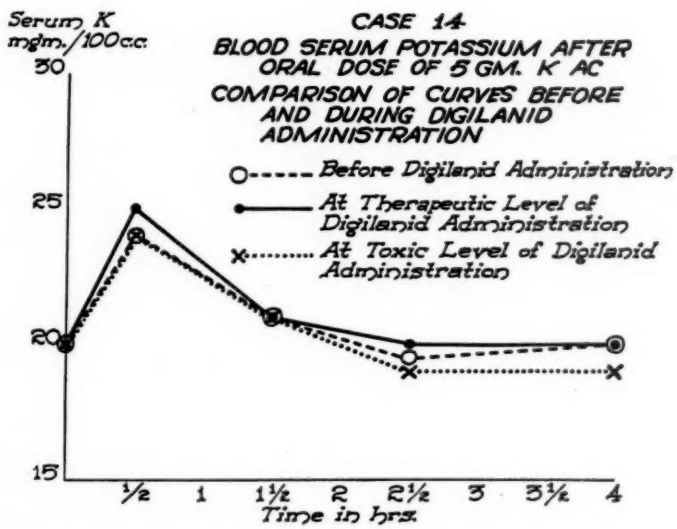

Serum K
mgm./100c.c.
CASE 14
BLOOD SERUM POTASSIUM AFTER ORAL DOSE OF 5 GM. K AC
COMPARISON OF CURVES BEFORE AND DURING DIGILANID ADMINISTRATION
O----- Before Digilanid Administration
——— At Therapeutic Level of Digilanid Administration
×..... At Toxic Level of Digilanid Administration
30
25
20
15
½ 1 1½ 2 2½ 3 3½ 4
Time in hrs.

Fig. 3.

insulin. He associated their occurrence with a low potassium content of the blood serum. The fasting potassium content of the blood serum in our series varied from 16 to 20 mg. per cent, and there was apparently no correlation between this level and the presence or absence of ectopic beats.

There is a suggestion that the relative rise of the serum potassium from the fasting level to that which existed one-half hour later had more effect on the ectopic beats than the absolute potassium content (Cases 2, 3, 7, 13, and 16).

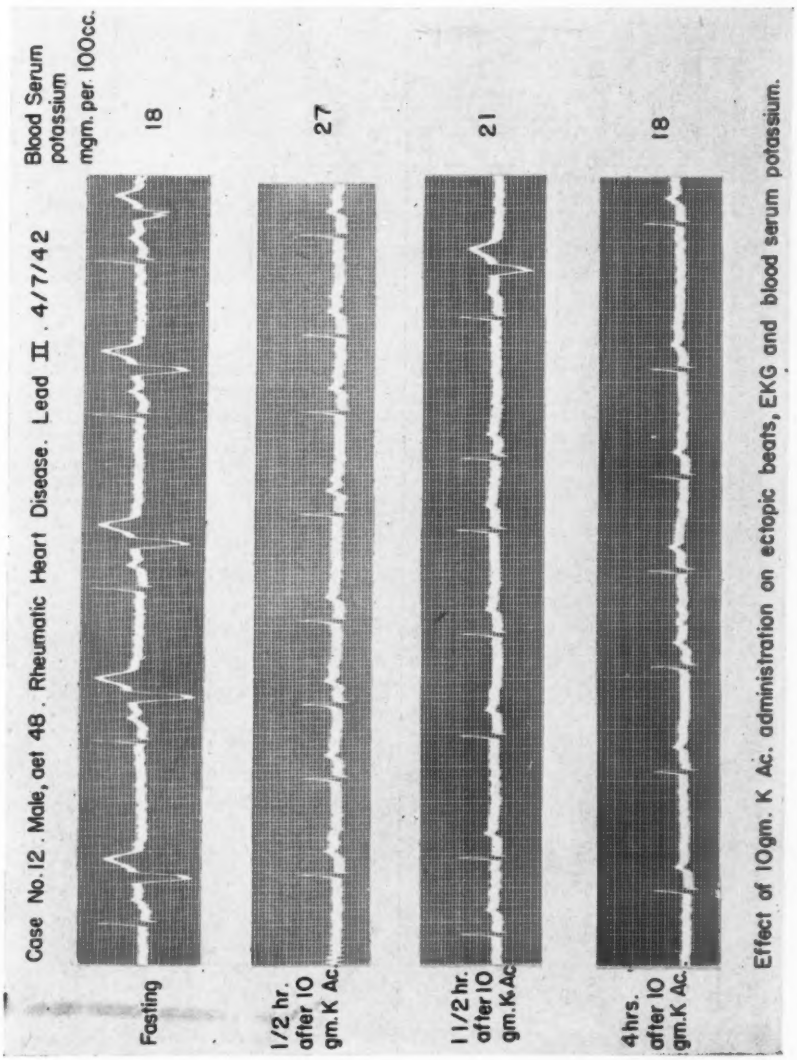

Case No. 12 . Male, aet 48 . Rheumatic Heart Disease. Lead II . 4/7/42
Blood Serum potassium mgm. per 100cc.
18
27
21
18
Fasting
1/2 hr. after 10 gm. K Ac.
1 1/2 hr. after 10 gm. K Ac.
4 hrs. after 10 gm. K Ac.
Effect of 10gm. K Ac. administration on ectopic beats, EKG and blood serum potassium.

Fig. 4.

In Case 12 (Fig. 4), after 10 Gm. of potassium acetate had been given, the ectopic beats disappeared in one-half hour, at which time the serum potassium was at the unusually high level of 27 mg. per cent. When it fell, at the end of one and one-half hours, to a level of 21 mg. per cent, the ectopic beats recurred, but disappeared again at the two and one-half hour and four hour periods, when the blood serum potassium content had resumed the fasting level. This was an instance

TABLE

A STUDY OF EIGHTEEN CASES ILLUSTRATING THE EFFECT OF POTASSIUM ON ECTOPIC BEATS

CASE	SEX	AGE	ETIOLOGY OF DISEASE	DATE	RHYTHM	DOSE OF DIGITALIS
1	L. C. Male	64	Coronary arteriosclerosis	8/5/41	Complete heart block (A-V)	Digld. 1 mg. daily × 12
2	J. L. Male	74	Coronary arteriosclerosis	8/15/41	Aur. fibrillation	Digld. 1 mg. daily 3+ weeks
3	M. G. Male	73	Coronary arteriosclerosis, hypertension	8/15/41	Sinus rhythm	Digld. 1 mg. daily 3+ weeks
4	T. L. Male	67	Coronary arteriosclerosis	8/6/41	Aur. fibrillation	Digld. 1 mg. daily × 10
5	J. O. Male	71	Coronary arteriosclerosis	8/29/41	Sinus rhythm	Digld. ½ mg. daily 3+ weeks
6	W. L. Male	71	Coronary arteriosclerosis	8/29/41	Sinus rhythm	Digld. 1 mg. daily × 25
7	W. B. Male	80	Arteriosclerosis and coronary occlusion	9/9/41	Aur. fibrillation	Digld. 1 mg. daily × 37
8	C. S. Male	72	Coronary arteriosclerosis	9/9/41	Aur. fibrillation	Digld. 1 mg. daily 3+ weeks
9	C. S. Male	83	Coronary arteriosclerosis, angina pectoris	10/3/41	Sinus rhythm	None
10	J. G. Male	79	Coronary arteriosclerosis	12/27/41	Aur. fibrillation	None
11	H. B. Male	77	Coronary arteriosclerosis, hypertension	10/14/41	Aur. fibrillation	None
				11/19/41	Aur. fibrillation	Digld. ½ mg. daily 3+ weeks
				12/13/41	Aur. fibrillation	Digld. 1 mg. daily × 24
12	F. S. Male	45	Rheumatic			Dig. Fol. 0.3 for 3 days and then
				11/10/41	Aur. fibrillation	Dig. Fol. 0.1 Gm. daily × 30
				1/13/42	Aur. fibrillation with bigeminus	Dig. Fol. 0.1 Gm. daily × 64
				4/5/42	Aur. fibrillation with bigeminus	Digld. 2 mg. daily × 3 and then Digld. 1 mg. daily × 14
				4/7/42	Aur. fibrillation with bigeminus	Digld. 1 mg. daily × 2
13	H. K. Male	76	Coronary arteriosclerosis ? rheumatic	10/14/41	Aur. fibrillation	None
						Digld. ⅝ mg. daily × 30
				11/19/41	Aur. fibrillation	Digld. ½ mg. daily × 14
				12/24/41	Aur. fibrillation	Digld. ½ mg. daily × 35
				4/6/42	Aur. fibrillation	Digld. ½ mg. daily × 60
						Digld. 1 mg. daily × 43

I

AND ON THE BLOOD SERUM WITH AND WITHOUT ADMINISTRATION OF DIGITALIS GLYCOSIDES

BLOOD SERUM POTASSIUM IN MG. PER CENT IN RELATION TO TIME OF POTASSIUM DOSE					NO. OF VENTRICULAR ECTOPIC BEATS PER MINUTE IN RELATION TO TIME OF POTASSIUM DOSE					POTASSIUM ACETATE DOSAGE
FASTING	½ HR. AFTER	1½ HR. AFTER	2½ HR. AFTER	4 HR. AFTER	FASTING	½ HR. AFTER	1½ H.R. AFTER	2½ HR. AFTER	4 HR. AFTER	
19	16	24	21	—	15	2	0	0		5 Gm. orally
17	25	22	20	—	7	12	0	7		5 Gm. orally
17	27	23	—	—	10	0	0	0		5 Gm. orally
16	18	19	16	—	6	0	0	0		5 Gm. orally
17	—	22	18	—	35	3	0	4		5 Gm. orally
—	—	—	—		12	0	0	0		5 Gm. orally
16	30	19	17.5	17	25	0	0	0	0	5 Gm. orally
17	15	26	17.5	17	22	0	0	7	10	5 Gm. orally
20	—	—	—	22	1 (Aur. ectopic beats only)	0	0	0	0	5 Gm. orally
23	27	30	25	22	0	0	0	0	0	5 Gm. orally
20	22	25	—	19	0	0	0	0	0	5 Gm. orally
19	—	26	—	20	1	0	0	0	0	5 Gm. orally
21	—	30	—	—	0	0	0	0	0	5 Gm. orally
18	20	21	—	—	20	2	8	6	0	5 Gm. orally
18	20.5	18.5	—	—	40	Abolished for 6 minutes only after potassium injection.				1 Gm. intravenously
18	20	20	—	18	Bigem.	Bigem.	Bigem.	Bigem.	Bigem.	5 Gm. orally
18	27	21	18	18	30	0	6	1	0	10 Gm. orally
17	26	25	19	18.5	3	1	3	2	0	5 Gm. orally
18	23	23	20	17	1	0	0	0	0	5 Gm. orally
17	23	19	18	17	0	0	0	0	0	5 Gm. orally
17	24	19	18	17	12	0	0	0	0	5 Gm. orally

TABLE I

CASE	SEX	AGE	ETIOLOGY OF DISEASE	DATE	RHYTHM	DOSE OF DIGITALS
14	A. M. Male	78	Coronary arteriosclerosis	11/13/41	Sinus rhythm	Digld. $\frac{3}{4}$ mg. daily × 3
				2/5/42	Sinus rhythm	Digld. $\frac{3}{4}$ mg. daily × 84
				3/24/42	Sinus rhythm	Digld. $1\frac{1}{4}$ mg. daily × 10
15	J. B. Male	77	Hypertension	11/23/41	Sinus rhythm	Dig. Fol. 0.3 Gm. for 3 days Dig. Fol. 0.1 Gm. daily for 4+ weeks
16	A. A. Male	80	Coronary arteriosclerosis, hypertension	12/13/41	Nodal rhythm (A. V.)	None
17	J. R. Male	64	Coronary arteriosclerosis	4/23/42	Aur. fibrillation	Dig. Fol. 0.3 Gm. for 3 days
				4/25/42	Aur. fibrillation	Dig. Fol. 0.1 Gm. daily 3+ weeks
				5/10/42	Aur. fibrillation	No digitalis 15 days
18	J. B. Male	62	Coronary arteriosclerosis, rheumatic	5/16/42	Aur. flutter	8 c.c. Digld. C. intravenously
					Aur. fibrillation Aur. flutter	4 doses of Digld. C. $\frac{1}{4}$ mg. each in 18 hours

of an apparent transient correlation of the blood serum potassium level with the loss of ectopic beats, but further confirmed the theory of later fixation of the potassium to the tissue. In all cases the ectopic beats had returned within sixteen hours. In one case (Case 12), giving 2 Gm. of potassium acetate in a 10 per cent solution intravenously caused the disappearance of ectopic beats for only six minutes, although the rise of potassium in the serum was not great.

Electrocardiograms were taken in most cases at approximately the same time as the blood specimens were obtained. In three instances studies were made before digitalis was administered, during the therapeutic period, and after the development of toxicity. In two other instances studies were made during the therapeutic period, either before or after the observations during a toxic phase. In Case 12 (Fig. 5), studies were made during repeated potassium administrations for forty-eight hours.

The electrocardiographic changes caused by the administration of potassium experimentally to cats (Chamberlain, et al.[17]), to dogs Winkler, et al.[16]), to guinea pigs (Spealman[18]), and to man (Sampson and Anderson,[1, 2] Stewart and Smith,[20] Thompson,[14, 15] Castleden,[10] and Keith, et al.,[56, 57]) include elevation of the T waves, auriculoventricular block, intraventricular block, and various arrhythmias.

The changes observed in this series were relatively minor. Ten patients showed slight elevation of the T waves, five showed flattening and depression of S-T intervals, and five showed minor changes in the

—CONT'D

BLOOD SERUM POTASSIUM IN MG. PER CENT IN RELATION TO TIME OF POTASSIUM DOSE					NO. OF VENTRICULAR ECTOPIC BEATS PER MINUTE IN RELATION TO TIME OF POTASSIUM DOSE					POTASSIUM ACETATE DOSAGE
FASTING	½ HR. AFTER	1½ HR. AFTER	2½ HR. AFTER	4 HR. AFTER	FASTING	½ HR. AFTER	1½ H.R. AFTER	2½ HR. AFTER	4 HR. AFTER	
20	24	21	19.5	20	0	0	0	0	0	5 Gm. orally
20	25	21	20	20	0	0	0	0	0	5 Gm. orally
20	24	21	19	19	0	0	0	0	0	5 Gm. orally
19	24	20	19	19	0	0	0	0	0	5 Gm. orally
18	25	19	18	19	7 (Aur. ectopic beats only)	3.5	0	8	0	5 Gm. orally
17	19	20	18	18	—	—	—	—	—	5 Gm. orally
18	22	20	19	18	5	2.5	1	0	5	5 Gm. orally
27	25	—	—	—	5	0	0	—	—	10 Gm. orally
17	24	—	20	19	0	0	0	0	0	5 Gm. orally
18	26	24	23	19	8	0.5	6	2	0	10 Gm. orally

voltage or direction of the QRS complexes. These occurred with about equal frequency before and after digitalis administration, and with (Fig. 6, Case 13) and without ectopic beat formation (Fig. 7, Case 14).

Another possible influence of potassium on the cardiac rhythm is illustrated by Case 18; the patient was a white man, aged 62 years, with rheumatic heart disease, who entered the hospital with auricular flutter. The flutter was supplanted by auricular fibrillation only after large doses of digilanid C intravenously and orally. Two and one-half hours after the administration of 5 Gm. of potassium acetate by mouth, the mechanism reverted to auricular flutter, with a variable degree (4:1 to 7:1) of auriculoventricular block. Not all of the ectopic beats had disappeared at this time. Four hours after the administration of potassium acetate, all of the ectopic beats had disappeared, and the flutter was regular, with 7:1 auriculoventricular block. Normal rhythm was later restored by giving 1 Gm. of quinine dihydrochloride intravenously.

Stewart and Smith[20] have recently reported certain toxic effects of the oral use of potassium chloride and potassium iodide in man which resemble those in dogs[16] and cats.[17] In some cases, doses of 2 to 8 Gm. per day produced auriculoventricular block, aberrant ventricular impulses, and auricular standstill.

Likewise, Arden[58] described paresthesias after 15 Gm. of potassium chloride or potassium carbonate had been given. This observation was confirmed by Keith, Osterberg, and Burchell,[56, 57] who used oral doses

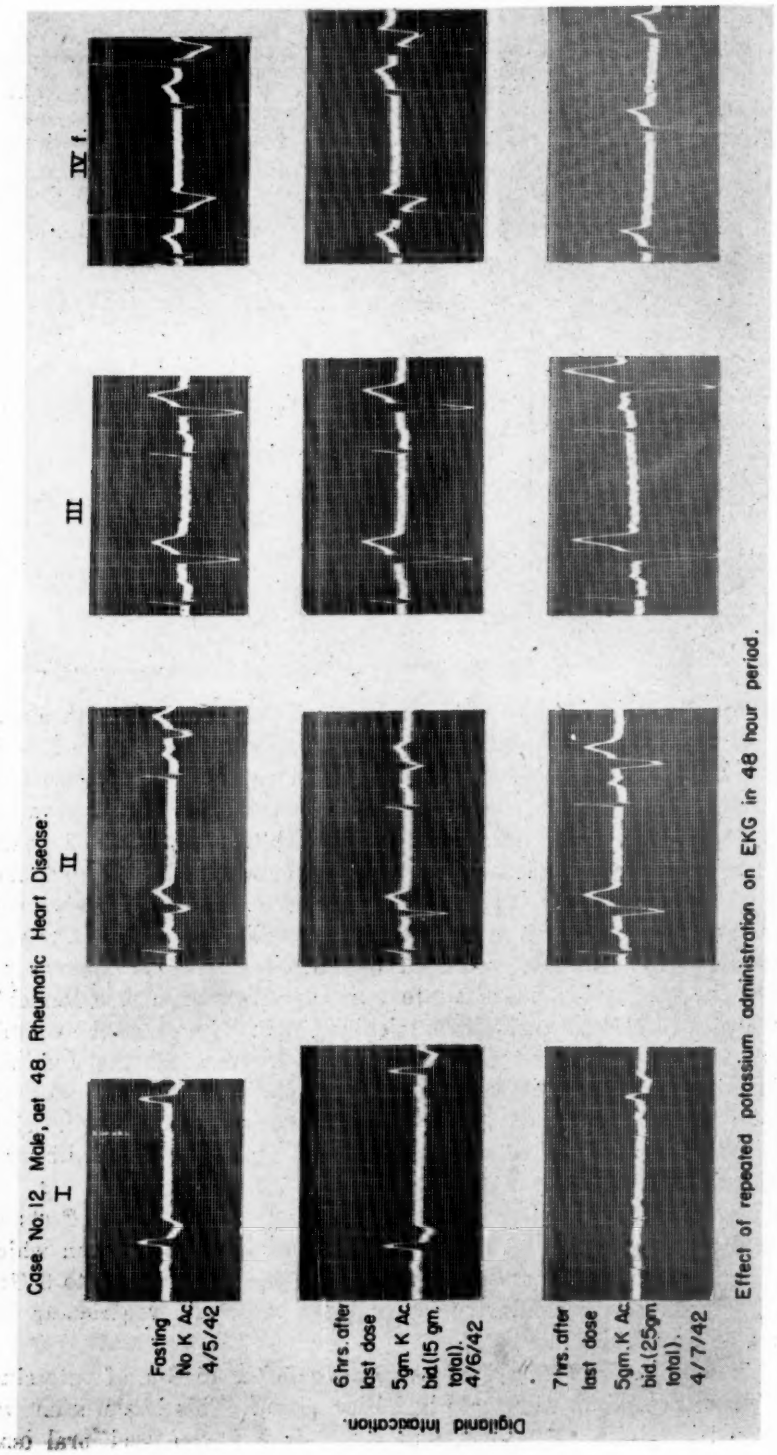
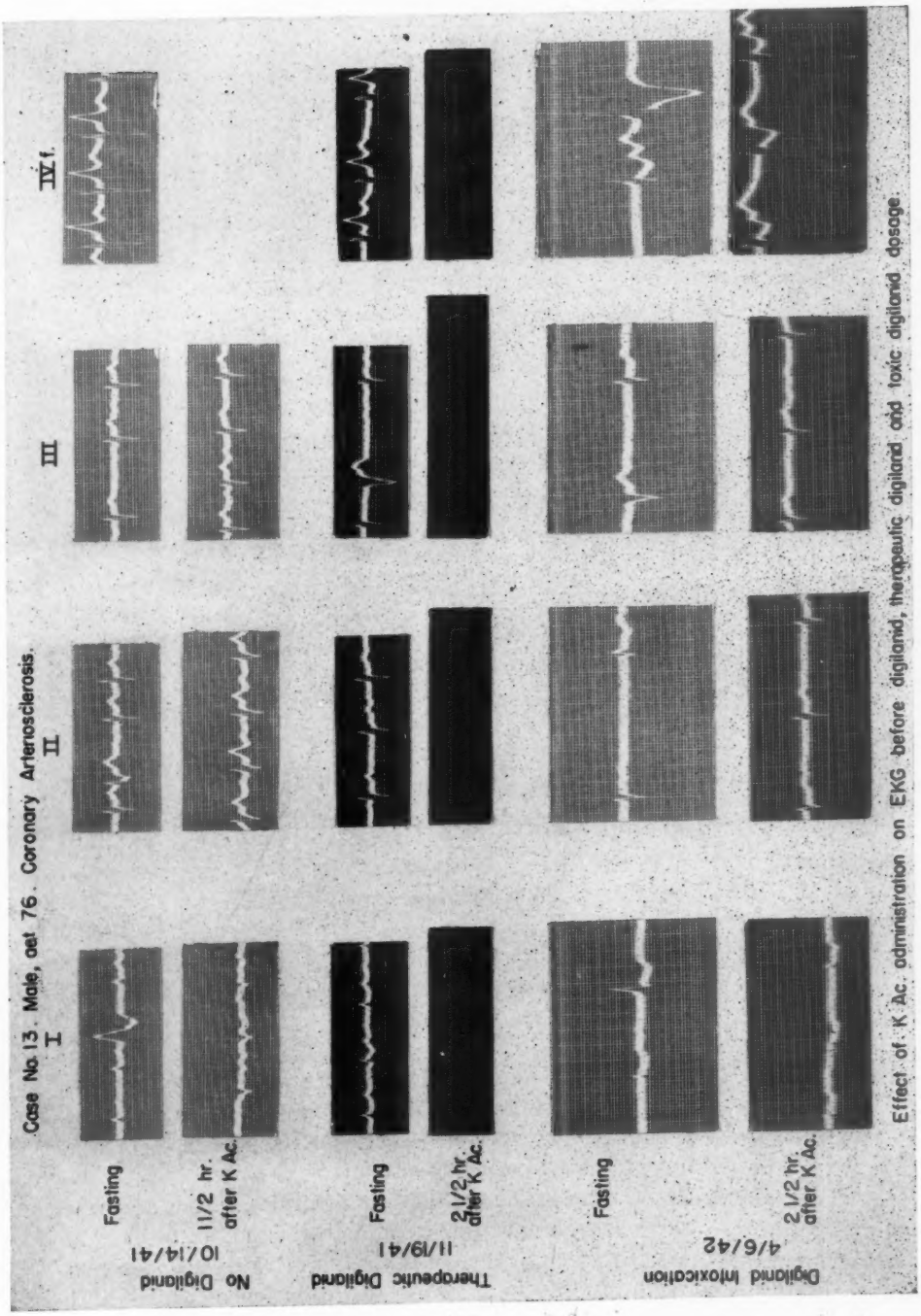

Case No. 12. Male, aet 48. Rheumatic Heart Disease.
Digitalis Intoxication.
I
II
III
IV f.
Fasting No K Ac. 4/5/42
6 hrs. after last dose 5gm. K Ac. bid.(15 gm. total). 4/6/42
7 hrs. after last dose 5gm. K Ac. bid.(25gm. total). 4/7/42
Effect of repeated potassium administration on EKG in 48 hour period.

Fig. 5.



Effect of K Ac. administration on EKG before digitalis, therapeutic digitalis and toxic digitalis dosage.

Fig. 6.

of 12.5 to 17.5 Gm. of potassium chloride, or potassium bicarbonate in an intravenous dose of 9.5 Gm. in a 1 per cent solution, administered over ninety minutes. They considered 30 mg. per cent of blood serum potassium as the level at which certain paresthesias appear. In one case, not included in our series because of lack of potassium studies, paresthesias preceded severe shock-like symptoms after a 5 Gm. dose of potassium acetate had been given intravenously. There have been previous reports of serious shock-like symptoms after the oral administration of potassium salts to patients with kidney disease (Smillie,[59] Wilkins and Kramer,[54] Blum,[60] Magnus-Levy,[61] and others). The absence of nitrogen retention and clinical manifestations indicated that none of our patients had severe kidney disease.

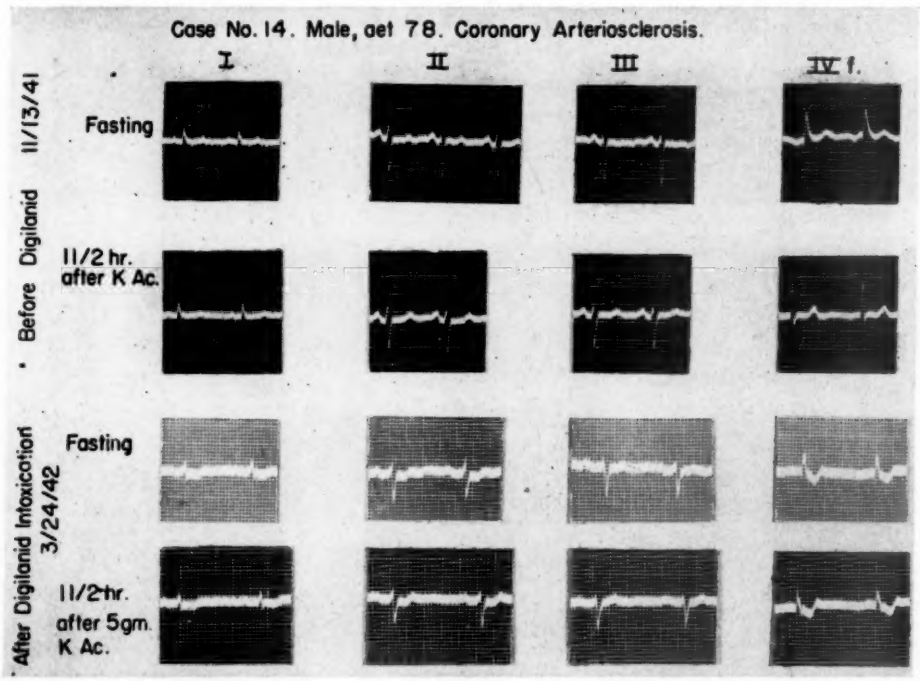


Fig. 7.

In the report of Sampson and Anderson[1, 2] there were three instances of a paradoxical action of potassium which increased the number of extrasystoles; this may be interpreted as a toxic phenomenon. These patients did not have digitalis intoxication.

In the present series of cases no signs of serious intoxication or paradoxical action occurred with the oral administration of 5 to 10 Gm. of potassium acetate, or in one instance after the intravenous injection of 1 Gm. of potassium acetate in a 10 per cent solution at a rate of 1 c.c. per minute. In one other instance, as previously mentioned, severe shock-like symptoms occurred after the injection of 10 c.c. of a 50 per cent potassium acetate solution at a rate of 1 c.c. per minute.

Although the purpose of this work was not to investigate the therapy of digitalis intoxication, it may be assumed that the oral administration of potassium salts will abolish ectopic beats, and probably paroxysmal ventricular tachycardia. Sampson and Anderson[1, 2] reported the cessation of paroxysmal ventricular tachycardia after potassium therapy in a patient with coronary arteriosclerosis who had not received digitalis, which suggests that potassium might be efficacious in the treatment of ventricular tachycardia caused by digitalis intoxication.

Although no amelioration of other toxic symptoms, e.g., nausea, was brought about by the use of potassium in this series of cases, the salts were administered for too short a time to draw any definite conclusion on this point.*

CONCLUSION

We have shown that the ectopic beats caused by digitalis can be abolished in every instance by the oral administration of potassium salts in doses of 5 to 10 Gm.; this is in contrast to the observation of Sampson and Anderson that only 50 per cent of ectopic beats from other causes were affected by potassium salts. We thus present positive evidence that the disturbance of potassium balance in the heart muscle is related to digitalis administration—at least in toxic doses.

There was no correlation between the presence or absence of ectopic beats and the fasting blood serum potassium level. No significant differences occurred in the curves of the potassium rise and fall in the blood serum in relation to oral potassium acetate doses at any stage before or during digitalis administration—even with toxic doses.

When ectopic beats were abolished by the administration of potassium, they failed to return in many instances until long after the blood serum potassium content had fallen to fasting levels. This suggests that potassium had become fixed to, or had altered the state of, the cardiac muscle, for the presence of ectopic beats, temporarily at least, was not influenced by the potassium content of the blood serum.

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EMBOLISM AND SECONDARY THROMBOSIS OF THE BIFURCATION OF THE AORTA

A. Coronary Occlusion With Endomyocardial Infarction
B. Mitral Stenosis With Atrial Fibrillation

George R. Herrmann, M.D., J. G. Willis, M.D.,
W. Frank McKinley, M.D., and Lester Karotkin, M.D.
Galveston, Texas

THE recognition of potential causes, precipitating factors, and especially of the secondary complications of progressive thrombotic processes, as well as the prompt diagnosis and localization of acute arterial obstruction, has come to a position of considerable importance now that prevention and treatment of the condition are much more promising. Cases of saddle embolus at the bifurcation of the aorta and embolism of the common iliacs and femoral arteries should be reported in detail, so that the etiologic factors and the clinical and the pathologic manifestations may be established clearly. Attention should be focused on the possible seriously complicating secondary thrombotic processes.

Secondary thrombosis is an essential consideration, whether conservative management or embolectomy be undertaken. The prompt use of antispasmodics (papaverine) intravenously, alone or with an anticoagulant (heparin), followed by passive vascular exercises (pavaex), may be immediately effective, and opening up of the major arterial pathways may be the result—a most spectacular therapeutic triumph. At least, the serious complications can often, in a large measure, be prevented.

Heparinization, to be effective, must be instituted before the secondary thrombosis takes place, and, certainly, as soon as possible after an embolus has lodged, in order to prevent the local development of thrombosis. This is particularly so in patients who are likely to have atheromatosis of the aorta. Immediate diagnosis is, therefore, of considerable importance. The prognosis is worse in cases of coronary thrombosis and hypertension than in patients with mitral stenosis.

The larger the embolus, the higher up in the vascular tree it lodges, and, the more completely it fills the lumen, the greater are the dangers of complications. In the presence of an effective heparin, liquaemin, or dicumarol action, conservative methods, such as the intravenous injection of papavarine (½ to 1 grain), as suggested by Denk, and passive vascular exercise, as employed by L. G. Herrmann, may be hopefully undertaken. This should yield results during the first six hours after the occurrence of embolism. Medical treatment should probably be instituted first in every case.

From the Departments of Medicine and Pathology of the University of Texas Medical School, and the Cardiovascular Service of the John Sealy Hospital, Galveston, Texas.

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Early diagnosis and localization are as important in successful surgical treatment as they are in conservative management. Embolectomy is most successful only within the first six hours, and, at the latest, twenty-four hours after the accident.

SUMMARY OF REPORTED RESULTS OF TREATMENT

Medical treatment, conservative and expectant, with morphine, whiskey, and pavaex therapy has been reported as successful. L. G. Herrmann[1] has had three successes with conservative management among several unpublished cases of saddle embolism. Morris[2] also reported success in a case of embolism of the bifurcation of the aorta in which pavaex therapy was started forty-eight hours after the onset. This may have been a spontaneous recovery.

Fry[3] reviewed 135 reported cases of embolism of the bifurcation of the aorta. In this series there were twenty survivals, of which ten were attributed to the development of collateral circulation. Nine recoveries were believed to have been the direct result of embolectomy, and one was attributed to the passage peripherally of the embolus.

Surgical removal of an embolus and subsequent complete restoration of the circulation has been successfully accomplished. In Sweden, up to 1936, 382 embolectomies had been performed, with 86 (22.5 per cent) recoveries; 69 patients (18.1 per cent) required subsequent amputation, and 227 (59.4 per cent) died in the hospital. Of the 17 patients with aortic embolism, 3 (17.7 per cent) were rescued, and of 66 with iliac embolism, 10 (15.1 per cent) were saved by operation. In England, up to 1937, there had been only 20 embolectomies, with only 11 (55 per cent) recoveries. These series were done before any anticoagulant was generally available. Since the introduction of heparin for clinical use, slightly over half of the first 100 patients operated upon have recovered.

Although the bifurcation of the aorta is less accessible than large peripheral arteries, it has been completely cleared of clots from below. In a young patient with mitral stenosis, McMaster[4] succeeded in removing emboli from both iliac bifurcations and re-establishing the circulation without the use of anticoagulants. McFarland[5] has successfully removed saddle emboli directly, and Ravdin and Wood[6] cleared the bifurcation of the aorta of clots indirectly, through the femorals, with the help of heparin.

Murray[7] reported sixteen surgical successes, with nine complete successes, in a series of seventeen embolisms in accessible major arteries. In Murray's series of thirty-seven cases of embolism, more than half of the emboli were lodged in the common femorals, and four were arrested at the bifurcation of the aorta.

PREDISPOSING FACTORS AND COMMON SOURCES OF LARGE PERIPHERAL ARTERIAL EMBOLI

Arterial embolism is a possible complication in any case of organic disease of the heart or aorta. It has long been recognized that especially

patients with the atrial stasis of mitral stenosis and atrial fibrillation, and those with verrucous valvulitis, are candidates for embolism. Mural thrombi that developed in the greatly dilated left auricle and ventricle during chronic failure are occasionally loosened and carried into the aorta as emboli. Mural thrombi that accumulate on the endocardium beneath recent myocardial infarcts are more common sources of emboli. The statistics of the incidence of arterial embolism from these various sources are as yet incomplete. All cases should be reported in order to accumulate data on the frequency of the condition.

Garvin[8] found mural thrombi in the heart in one-third of all cases in which death was caused by congestive heart failure, and in two-thirds of the hearts with myocardial infarction, in a study of 771 consecutive autopsies on patients who died of heart disease.

Solandt, Massil, and Best,[9] on the premise that 10 per cent of the deaths of patients with coronary thrombosis were caused by embolism as a result of mural thrombus formation, undertook experiments on dogs. They studied mural thrombus formation that resulted from ligation of the anterior descending branch of the left coronary artery and subsequent injection of sodium ricinoleate into the left ventricular cavity. They found that in such experiments mural thrombus formation could be regularly prevented entirely by the use of heparin.

Embolism from the left side of the heart to the aortic bifurcation, along with secondary local thrombosis, was recognized by Allibert, in 1828, and by Alexander, in 1905, and elaborated upon by Welch, in 1909. Welch's[10] series consisted of 59 cases; in 35, the heart was the source, and, in 20 of these, rheumatic mitral stenosis was present; whereas, in 3, acute mitral endocarditis was the primary etiologic factor. Hesse,[11] in a review of the literature on 72 cases up to 1921, considered embolism and thrombosis of the bifurcation of the aorta together. Rothstein,[12] in 1935, reviewed the literature on 125 cases of saddle embolism of the aorta. He added 5 cases of his own in children following acute infections, one from iodoform poisoning, and one from tumor pressure.

Mural thrombi of the aorta have been considered generally as rare sources of embolism at the aortic bifurcation, but in several of Welch's,[10] Hesse's[11] and Rothstein's[12] cases the emboli came from the aorta or an aneurysm, or were caused by a mycotic aneurysm, tumor pressure, or atheromatosis. Thrombi in the thoracic aorta are more common sources of embolism of the superior mesenteric or the renal arteries, as well as of the arteries of the lower extremities. Thrombi on the endocardium of the right ventricle, as well as from the great veins, may give rise to embolism of the pulmonary arteries, and cause acute cor pulmonale.

THE CLINICAL PICTURE

Premonitory symptoms may occur as a large embolus migrates down the aorta, and may well be watched for in patients who are predisposed to such complications. *Abdominal cramps* at higher, then lower,

levels, with nausea, vomiting, meteorism, and constipation, may indicate temporary closure of the mesenteric and renal orifices. After localization, the clinical picture is quite characteristic, especially if there is sudden and complete occlusion in a major arterial pathway. The sudden onset of *pain,* localized to the region of the obstruction, is the first symptom. The pain is not always excruciating, but is frequently severe, and produces what seems to be temporary paraplegia; occasionally it is moderate in character. In cases of only partial obstruction of large vessels, such as the iliacs or the aorta at the bifurcation, the immediate local pain may be mild, and, in stolid persons, may go unrecognized. It is practically impossible to differentiate between embolism and thrombosis at the aortic bifurcation. If the obstruction is fairly complete, paresthesias, tingling, formication, *numbness,* and *coldness* are usually felt in the extremities, beginning at the distal ends and migrating upward as far as the level of the iliac crests. Later on, with the numbness and coldness, there is pain. Contraction of the leg muscles is often accompanied by pain which is relieved by rest, as in intermittent claudication.

The *color changes* occur promptly below the site of the embolus. Striking pallor appears immediately in the distal parts. There is cadaveric whiteness, and the skin takes on a somewhat waxy appearance. As one proceeds up the extremity from the tips of the digits, a zone of dark cyanosis is noted on the pallid background. Above this there is a zone of mottled skin, with patchy, pallid, and purplish areas which extend to the level of the embolus.

When the embolus is lodged at the bifurcation of the aorta, color changes are present as high as the lower quadrants of the abdomen. If the embolus is at the common iliac bifurcation, color changes extend into the upper third of the thigh; if in the common femoral bifurcation, color changes reach the lower two-thirds of the thigh; if in the popliteal bifurcation, the color changes appear between the ankle and the knee; if in the posterior tibial artery, color changes are limited to the heel and the plantar surface of the foot below the instep.

A lowered skin temperature is noted on palpation. Usually the skin is stone-cold to the touch. Variations of coolness are observed up to the level of the occlusion. Absence of pulsation in the dorsalis pedis, posterior tibial, popliteal, and femoral arteries of both legs and a zero *oscillometric index* in both legs and thighs result from saddle embolism or thrombosis of the bifurcation of the aorta or both common iliacs.

The *skin sensitivity* is reduced. The reflexes are decreased or absent, and voluntary control of the movements of the toes is lost. A saddle embolus may produce complete obliteration on one side and only partial obstruction of the other iliac. A murmur may be heard over a partially obstructed artery. Small fragments may break off of the main embolus and lodge at a bifurcation further distally, especially when the main artery is only partially obstructed.

When occlusion of an artery by an embolus is incomplete, the diagnosis may be most difficult, as one might expect. In such cases the disease frequently goes unrecognized clinically unless particularly looked for. In two of Fry's[3] cases the diagnosis was not made until months after the onset. In a third case it was found unexpectedly at autopsy.

OUR CLINICAL MATERIAL

Data on five cases of saddle embolus at the bifurcation of the aorta, with one recovery, and complete autopsy studies in three cases are herewith presented. The first two cases were in elderly males with hypertensive arteriolar disease, atheromatosis, coronary thrombosis, endomyocardial infarction, and mural thrombi. These gave rise to emboli which lodged at the bifurcation of the atheromatous aortas, followed by secondary thrombosis. The intra-aortic thrombosis extended backward practically to the levels of the renal arteries, and distally into the iliacs.

The third case was that of an elderly woman with rheumatic mitral stenosis and insufficiency, atrial fibrillation, vegetative endocarditis, hypertensive arteriolar disease, and mural thrombi in all of the heart chambers. An embolus, probably originally from the left atrium, saddled the bifurcation of her aorta. Marked arteriosclerosis of the aorta near the bifurcation apparently was responsible for prompt, massive, secondary thrombosis.

The last two cases were in younger persons with rheumatic mitral stenosis and insufficiency and atrial fibrillation. They apparently had less aortic disease and apparently survived longer after the emboli lodged at the aortic bifurcation. Both subsequently had cerebral embolism; one died and one survived. Conservative medical treatment was used in all instances. Heparinization and surgical intervention would probably have been successful in some of the cases.

CASE REPORTS

CASE 1. *Coronary Occlusion, Transient Atrial Fibrillation, Endomyocardial Infarction, Mural Thrombosis, Saddle Embolism of the Bifurcation of the Aorta, With Secondary Thrombosis and Gangrene of the Right Foot, Encephalomalacia.*—J. B., No. 36370, a 36-year-old Negro, was admitted to the John Sealy Hospital March 31, 1941, complaining of severe substernal pain radiating down the left arm; the pain had lasted for two hours. The patient was in shock, and was sweating, prostrated, cold, and clammy; his blood pressure was 90/50. His heart was apparently not enlarged. The heart sounds were distant. The abdomen was negative. The liver was not enlarged or tender. There was no edema.

The electrocardiogram confirmed the clinical diagnosis of coronary thrombosis, with posterior myocardial infarction. The cardiac mechanism, which was normal on first examination, changed within half an hour after admission to atrial fibrillation, with many ventricular ectopic beats. Within three hours after quinidine therapy was begun (total dose, 13½ grains), regular sinus rhythm was re-established. The evidences of shock decreased. The blood pressure rose to 110/90; pure oxygen had been given through an aviator's mask during this time.

Small doses of morphine were required occasionally during the first three days for relief of chest pain. For several days after admission there was some difficulty with gaseous abdominal distention. No signs of congestive heart failure developed at this time, and the first two weeks of his course were fairly uneventful.

On the morning of April 16, he began complaining of pain of rather sudden onset in the abdomen and right flank, and of numbness of the toes, and coldness of the feet. Examination showed marked abdominal distention; there was definite tenderness in the costovertebral angle. Coolness of the skin of the lower extremities, especially below the knees, was conspicuous. No pulse could be felt in either femoral artery. The sense of touch, pain, temperature, and position was not impaired, and there was no paralysis. The diagnosis was left ventricular mural thrombosis, from which an embolus arose and lodged at the bifurcation of the aorta.

On April 18, oscillometric studies showed no pulsation in either thigh or leg. There had been increasing pain in the thighs and the coldness below the knees became more pronounced. Paravertebral sympathetic block was not effective in relieving pain or in restoring warmth to the leg. By the next day the pain had become relatively slight, but numbness of the toes and marked coldness of the legs below the knees persisted. The body temperature increased from normal to as high as 102° F. on April 18.

During the next four weeks the patient's course was rather uneventful. There was minimal pain in the legs, with no ulceration or gangrene. However, he continued to have a low-grade fever, reaching 101° F., rectally, daily for a week; thereafter his temperature rose only slightly above 100°. Secondary thrombosis at the bifurcation of the aorta was suspected, but there was no clinical proof of extension of the process.

On May 19, postural exercises were instituted. On May 25, he developed a temperature of 103°; on May 26, his oral temperature reached 105°, and there was marked swelling of the right leg. On May 27, he suddenly complained for the first time of marked dyspnea, and died within a few minutes.

Summary of Pathologic Charges (Autopsy No. 5424).—The right leg was swollen and dark purple in color, and the epidermis lay loosely on the underlying tissue. Rigor mortis, which was present elsewhere, was absent from this leg. There was slight clubbing of the finger tips. The left pleural cavity was obliterated by fibrous adhesions; the right pleural cavity contained only a few fibrous adhesions. The pericardial sac contained 50 c.c. of clear yellow fluid.

The heart weighed 370 grams. The myocardium was flabby (Fig. 1). On cut section the posterior wall and apex of the left ventricle presented a mottled appearance, with areas which were yellow, dark red, and gray. Attached to the left ventricular endocardium over these infarcted areas there was a large, friable, red and gray thrombus. The coronary ostia were patent, but greatly narrowed by atherosclerotic and syphilitic changes. The interventricular branch of the left coronary artery was occluded by a large, firm, gray thrombus, located 1 cm. from the ostium. The circumflex branch was narrow, but patent; its intima bore a few atheromatous plaques. The right coronary artery contained a linear, firm, adherent, yellowish-gray thrombus. The thrombus did not occlude the lumen, but it extended into, and occluded, the interventricular branch of the artery.

The arch of the aorta presented longitudinal wrinkling and scattered stellate scars on the intimal surface, i.e., advanced syphilitic changes. There was moderate atherosclerosis which was most pronounced in the lower portion of the aorta. The lumen of the last 10 cm. of the abdominal aorta was occupied by a dark, red and gray, friable thrombus which was attached to the intima. This was more extensive as traced downwards, and completely occluded the aorta only at the bifurcation. The thrombus extended into both common iliac arteries, and from these into both internal and external iliac arteries. Separate from this thrombus there was a ring-

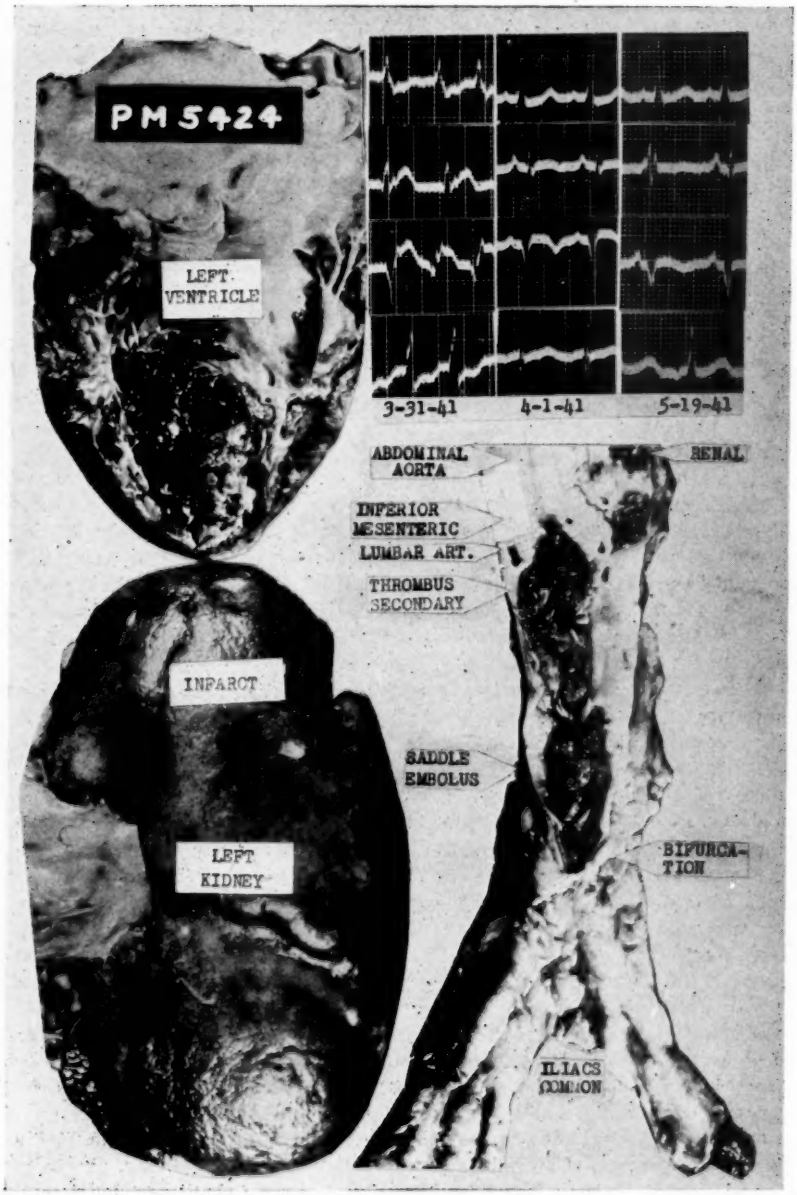


Fig. 1.—Case 1. J. B., J. S. Hospital, No. 36370; Post Mortem, No. 5424.

Right upper: Electrocardiograms from above downward (Leads I, II, III, and IV F): March 31, 1941, showing atrial fibrillation and evidences of acute posterior myocardial infarction; April 1, 1941, normal sinus mechanism after 20 grains of quinidine sulfate, elevated S-T_2 and S-T_3, with negative T_2 and T_3; May 19, 1941, persistence of some residua of the posterior myocardial infarction.

Left upper: Aorta and left ventricle opened up to show the mural thrombus and the thinned myocardium.

Left lower: The infarcted left kidney.

Right lower: The aorta with the thrombus extending from 10 cm. above the bifurcation into both common iliacs.

shaped thrombus attached to the intima of the aorta around the origin of the left renal artery. The right common iliac vein also contained a thrombus. The splenic artery contained a thrombus near its origin, but was not completely occluded; the spleen did not show evidence of infarction. Microscopic sections of the aorta showed fragmentation of the elastic tissue of the media, vascularization of the media, and perivascular round cell infiltration of the adventitia, all of which are characteristic of advanced syphilitic aortitis. Sections of the iliac vessels showed that the thrombi were undergoing beginning organization; there was an acute inflammatory reaction about the vessels.

The right lung weighed 600 grams; the left, 580 grams. Both were markedly edematous and showed gross and microscopic evidence of chronic passive congestion. No emboli were demonstrable in the pulmonary arteries. The liver weighed 1,580 grams and showed marked chronic passive congestion. The right kidney weighed 210 grams, the left, 200 grams. Both kidneys appeared to be congested. Their cortical surfaces were roughened by many depressed scars, the largest of which measured 2 cm. in diameter. On cut section, the areas corresponding to the scars showed yellowish mottling. The corticomedullary line was indistinct. Microscopic section revealed old and recent areas of infarction. In the noninfarcted areas there was advanced arterial and arteriolar nephrosclerosis. The sclerosis of the arteries and arterioles was very pronounced.

The brain weighed 1,350 grams. The frontal poles appeared atrophic. The basal vessels were sclerotic. On section, both lateral ventricles were slightly dilated. In the right hemisphere, extending from the middle portion of the temporal lobe toward the occipital pole, there was a large area of old softening which involved the hippocampal, lingual, and lateral occipital gyri. The left hemisphere also showed a softened area; it was less extensive than that on the right, and involved, mainly, the lateral surface of the occipital lobe. On microscopic examination both softened areas showed organization and extensive scavenger cell formation. No emboli were demonstrable in the cerebral arteries.

CASE 2. *Coronary Occlusion, Endomyocardial Infarction, Mural Thrombosis, Saddle Embolism of the Bifurcation of the Aorta, With Secondary Thrombosis, Gangrene of the Right Foot, Massive Infarction of the Kidneys, Uremia.*—R. F., No. 72578, a 47-year-old white man, an oil field worker, was admitted to the John Sealy Hospital, Sept. 8, 1941. He had considered himself in good health until July 13, 1941. At that time he developed severe precordial pain radiating to his left arm. The pain lasted about one day, and required several hypodermic injections of morphine for relief. This treatment was carried out in a hospital in his home town. One week after the onset of the cardiac pain, he developed a cough and high fever, and was thought to have pneumonia. There was no hemoptysis. Two weeks after the onset of his pain he developed coldness and pain in his left leg. This was followed within a day by similar pain and coldness in his right leg. He was told that his symptoms were due to "milk leg." However, there was never any considerable swelling of either leg at any time. Coldness and slight pain persisted in both legs intermittently thereafter. The symptoms would become quite mild and tolerable as long as the patient remained in bed, but any attempts to get up caused an increase in pain.

Two weeks before his attack of cardiac pain, and about three weeks after the onset of the pain in his legs, there was a marked increase in the pain in his left foot; this subsided somewhat six weeks after the onset of the trouble, one week before admission. Pain, coldness, and blueness became severe in his right leg. The symptoms in his right foot continued, and, twenty-four hours before admission, it was noted that his whole right foot was stony cold and of a deep purple color. Large doses of morphine had been required in the twenty-four hours before admission to control the pain.

After the second day of his illness the patient had no further chest pain. There was no dyspnea at any time, or any history of congestive failure or angina pectoris previous to July 13. There was no family history of cardiovascular disease. No past history suggestive of peripheral vascular disease was elicited.

Physical examination on admission showed a slightly obese, lethargic (morphine), mildly disoriented, acutely ill, middle-aged white man with a temperature of 100° F., pulse rate of 90, respiration rate of 22, and blood pressure of 158/96. Examination of the head and neck was negative. The fundi were negative. The neck veins were not distended. The heart showed no appreciable enlargement to percussion. The tones were of good quality. No murmurs were heard. There was no gallop rhythm. The pulse was regular. Examination of the lungs was negative. Abdominal palpation was likewise negative. The liver was not palpable.

The extremities showed much evidence of disease. The right foot was slightly swollen. A fairly sharp line of demarcation was present between the blue and white skin just above the ankle. Sensitivity to touch and pain was present down to, but not including, the tips of the toes. The left foot was warm; it was somewhat paler than normal, although there was some faint pinkness of the skin. On first examination, no pulse could be felt in the dorsalis pedis, posterior tibial, or femoral arteries. Very careful palpation showed what was thought to be a faint femoral pulse bilaterally. The oscillometric indices were very low in the thighs and absent in either calf.

The electrocardiograms were of the Q_2, T_2, Q_3, T_3 type, indicating residua of posterior myocardial infarction. On admission, there was only slight albuminuria. The erythrocyte count was 4,820,000, the leucocyte count, 9,450, and the hemoglobin, 76 per cent. The differential leucocyte count was normal. The Wassermann reaction and Eagle flocculation tests were negative. The blood urea nitrogen was 18 mg. per cent.

The patient was treated by paravertebral injection of the lumbar sympathetics. Ten c.c. of a 1 per cent novocain solution were injected into the second, third, and fourth lumbar spaces on the right. There was possibly very slight relief of pain after the injection. Pavaex therapy was used for twelve to fifteen hours a day on the right leg.

After several days it became quite obvious that attempts to save the right foot were futile, and amputation was done in the midthigh region. On Sept. 19, it was noticed that there were a large, bluish-red discoloration and considerable tenderness of the skin over the right buttock and sacrum. This lesion finally broke down and became a large decubitus ulcer.

The amputation stump healed satisfactorily without infection. There was some coldness of the left foot postoperatively, but this disappeared when the patient's state of shock was overcome. Throughout his hospital stay he ran a low-grade fever, with some increase from the time his decubitus infection started until a drainage of the ulcer was established. He experienced no recurrence of the pain in his chest. There was no evidence of congestive failure at any time during his hospital stay.

On Oct. 2, 1941, two weeks after operation, he rather suddenly developed a cramping abdominal pain, associated with nausea and vomiting. The symptoms at the time were considered to be suggestive of mesenteric embolism. There was, however, no diarrhea or melena, and migration of a large saddle embolus in the lower aorta was suspected. The abdominal pain subsided promptly after the administration of 1 grain of codeine and 10 grains of aspirin. On Oct. 6 the patient developed rather marked pain in his back, first in the left lumbar region, and later bilaterally. Then he suddenly became uremic, and the blood urea nitrogen rose to 150 mg. and the nonprotein nitrogen to 200 mg. per cent. On Oct. 17, the patient passed approximately 500 c.c. of highly colored, cloudy urine which

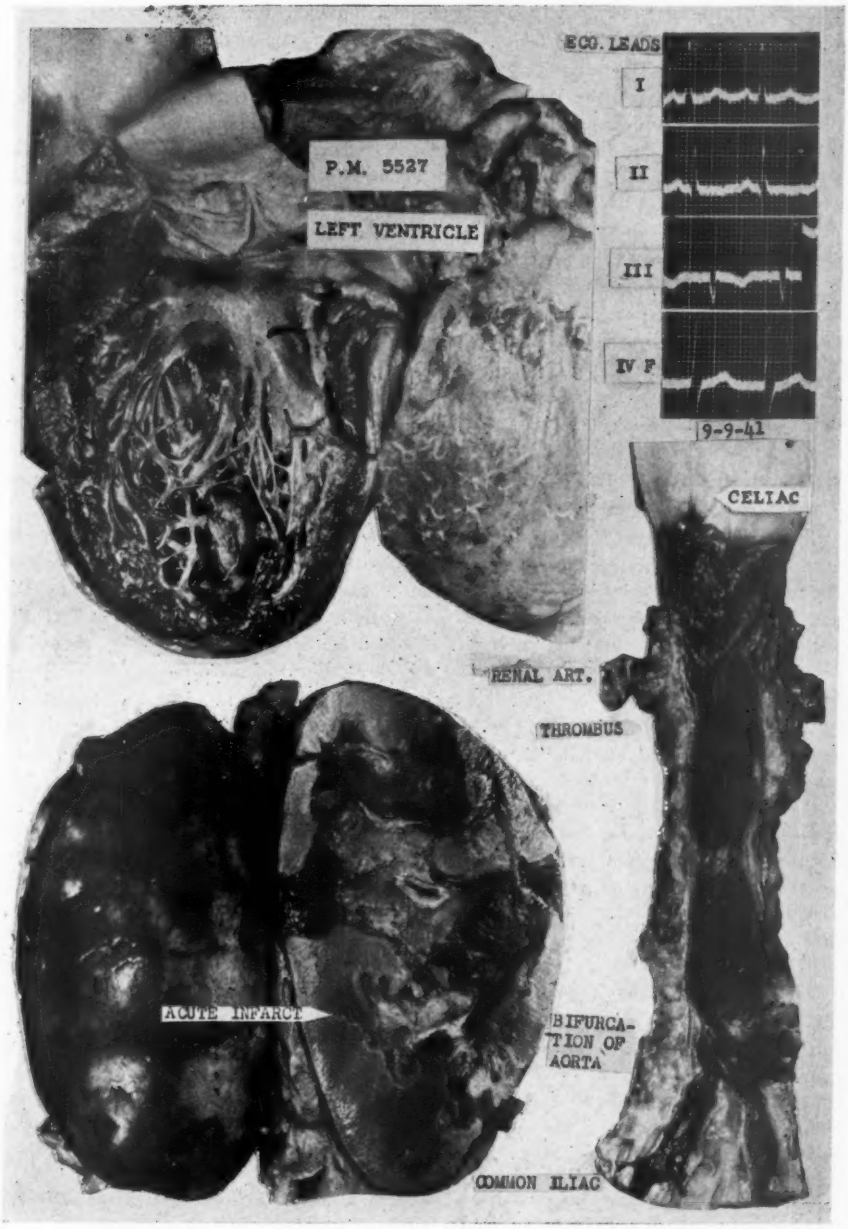


Fig. 2.—Case 2. R. F., J. S. Hospital, No. 72578; Post Mortem, No. 5527.
Right upper: Electrocardiogram showing residua of posterior myocardial infarction; Q_2 and Q_3 and slightly negative T_2 and sharply negative T_3.

Left upper: Aorta and left ventricle opened to show the mural thrombus and thinning of the muscle wall.

Left lower: The massively infarcted right kidney.

Right lower: The aorta containing the thrombus, extending from the celiac artery level into the common iliacs, especially on the right.

contained much albumin. This was virtually all the urine passed from Oct. 6 until his death, in uremia, without convulsions, on Oct. 20.

Summary of Pathologic Changes (Autopsy No. 5527).—The right leg had been amputated. There was sloughing over the right buttock and sacral region, with slight pitting edema of the left leg. The pleural cavities contained numerous thin fibrous adhesions which were easily broken down. The pericardial sac contained 300 c.c. of clear straw-colored fluid. The pericardial surfaces were covered with a thin layer of partially organized plastic exudate. The peritoneal cavity contained 1,400 c.c. of clear straw-colored fluid. There was generalized arteriosclerosis.

The heart weighed 440 grams (Fig. 2). All of the chambers contained mural thrombi. The thrombi in the ventricles were firmly attached to the endocardium at the site of a healing infarct involving the apices of both ventricles. The coronary arteries were somewhat narrowed by numerous atheromatous plaques, but nowhere was there an occluding lesion of a coronary artery. The myocardium showed patchy fibrosis.

The lungs showed moderate edema and marked hypostatic congestion. There were two small, white, firm, subpleural nodules near the hilum of the left lung; microscopically, these proved to be old infarcts in an advanced state of healing.

The liver weighed 1,390 grams, and presented gross and microscopic features of chronic passive congestion and fatty metamorphosis.

There was a large, partially organized thrombus in the aorta, extending from just below the celiac artery to the bifurcation of the aorta, and into both common iliac arteries to their bifurcations. The thrombus was firmly attached to the posterior wall of the aorta and did not occlude the lumen entirely, so that the mesenteric arteries presumably had an adequate blood supply. The thrombus reached into both renal arteries, apparently occluding them.

The right kidney weighed 250 grams; the left, 150 grams. The perirenal fat on both sides contained patches of fibrous tissue which was firmly adherent to the renal capsules. The surface of each kidney presented a mosaic appearance; there were sharply demarcated areas of bluish-red, yellow, and bright red discoloration. On cut section, very little normal tissue was seen in either kidney. The pelves and ureters presented a few petechiae. Microscopic sections of the kidneys showed large areas of coagulation necrosis, separated from the adjacent parenchyma by wide, irregular zones of granulation tissue. In the necrotic areas there were large blood vessels containing partially organized thrombi which were attached to the intima. The adjacent nonnecrotic parenchyma appeared edematous, and contained a few scattered hyalinized glomeruli. There were small, scattered, loose collections of lymphocytes. The large and medium-sized arteries showed uniform thickening of their walls.

The brain weighed 1,550 grams. The subarachnoid spaces were obliterated; the gyri were widened and the sulci narrowed. Microscopic sections of the brain showed marked edema. Sections of the brain prepared in xanthydrol solution showed the deposition of an abundant amount of xanthydrol urea. (This test is used frequently in cases of suspected uremia to show the high urea content of the tissues.)

CASE 3. *Rheumatic Mitral Disease, Hypertensive Arteriosclerotic Heart Disease, Atrial Fibrillation and Thrombosis, and Embolism at the Bifurcation of the Aorta and Secondary Thrombosis. Congestive Heart Failure.*—Mrs. K. H., No. 29858, a 57-year-old housewife, was admitted to the surgical service of the John Sealy Hospital. She was discharged June 25, 1942. She had had nausea and pain in the lower abdominal midline scar region, and had had no bowel movement for three days. At that time she was given Wangensteen suction treatment. She began to have bowel movements, and had one or two every day thereafter. However, nausea persisted.

She was readmitted to the hospital July 4, 1942 with the complaint of pain, coldness, and numbness in the legs. Five days prior to admission, on June 29, she had developed a sudden severe pain in the right calf. This came on about 4 o'clock in the afternoon, when she was walking from the bathroom. This pain was continuous in character and persisted until about noon the next day, when she had another severe pain, this time in the left calf. The pain in the right calf persisted, but was less severe. After that the patient had almost continuous pain in the calves of the legs. The feet had felt cold for four days, and for two days numbness had been noted, especially on the right.

She gave a history of having had dyspnea on exertion, such as going up and down stairs, for three weeks. She had no nocturnal dyspnea, precordial pain, or palpitation. Two weeks before admission nausea had begun, and she also had pain which was made worse by bending the body in the upper lumbar region. She had noticed swelling of her feet.

Physical examination on admission revealed a very obese, middle-aged white woman who was moderately dyspneic. She was alert and cooperative. She was lying flat on her back. Her left eyeball was missing. The right pupil was constricted, but the patient had had morphine previously. The heart was slightly enlarged to the left. The rhythm was grossly irregular. The rate was 90. There were no thrills, and no murmurs were heard. The blood pressure was 200/100. Examination of the lungs revealed a few fine moist râles at the right base and also at the left base anterolaterally.

The abdomen was protuberant. A ventral hernia was present in an operative scar in the lower midline. The liver was down 3 or 4 fingerbreadths below the right costal margin, and there was tenderness in the right costovertebral angle.

Examination of the extremities revealed that the skin of the thighs was cool, and that the legs and feet were cold. There was slight cyanosis of the feet and nail beds. The deep reflexes were decreased. No pulsation could be felt in the dorsalis pedis, posterior tibial, popliteal, or femoral arteries bilaterally. Oscillometric studies revealed no pulsation in the left or right thigh or in the lower part of the legs. The venous pressure was 17.5 cm. of saline. The circulation time was 15 seconds with magnesium sulfate and 25 seconds with ether.

Electrocardiograms revealed auricular fibrillation, with a rapid ventricular rate and definite evidence of myocardial damage.

Urinalysis revealed no significant abnormalities. The blood studies showed no anemia, but a slight polymorphonuclear leucocytosis. The nonprotein nitrogen was 40 mg. per cent, the urea nitrogen, 18.8 mg. per cent, the uric acid, 4.5 mg. per cent, and the creatinine, 0.91 mg. per cent.

The patient's course in the hospital was uneventful. She was kept at rest in bed, and given morphine to control the pain. She was given 3 grains of digitalis twice for one day, and then 3 grains daily.

On July 6 the blood pressure was 180/68. She refused food all day and was unable to void. Five hundred twenty-five c.c. of dark urine were obtained by catheterization. No pulsation could be felt in any of the arteries of the lower extremities, and fecal material obtained by digital examination of the rectum was strongly positive for blood. It was felt that this patient also had mesenteric embolism and infarction.

On July 8 the patient appeared much worse, and cried out almost constantly. The blood pressure was 195/108. The urine output was only 150 c.c. that day. The pulse rate was 70. On July 9, the patient was in about the same condition. On July 10 she was reported to have turned over and fallen out of bed at 6 o'clock in the morning. She was put back in bed and soon after that she was cyanotic, dyspneic, clammy, and perspiring freely. She was given ⅙ grain of morphine. No pulse could be felt, and the blood pressure could not be measured. She was restless,

complained of pain in the abdomen, legs, and head, and was groaning. She died approximately an hour after she fell out of bed.

Summary of Pathologic Changes (Autopsy No. 5672).—On external examination there was little of significance except that the right leg appeared to be of slightly greater diameter than the left. Opening of the body cavities revealed many fibrous adhesions in the pelvis and about the gall bladder and splenic regions.

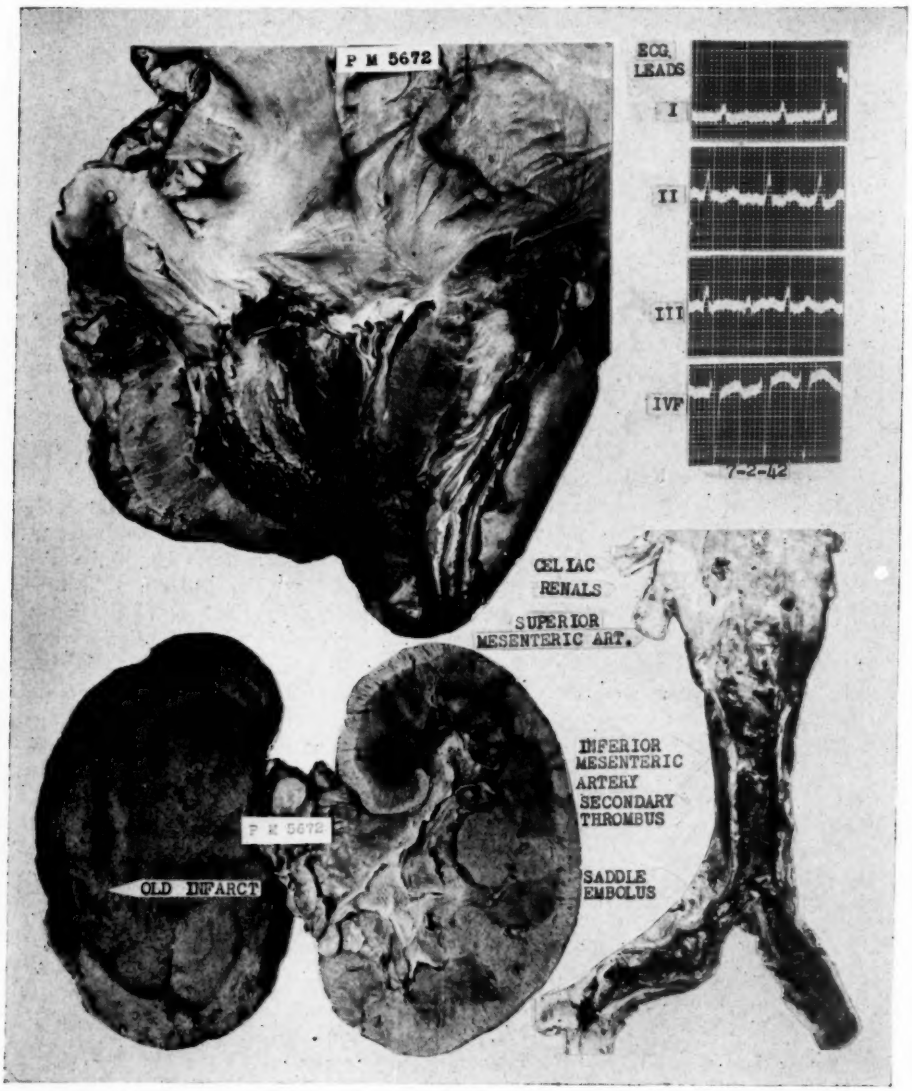


Fig. 3.—Case 3. Mrs. K. H., J. S. Hospital, No. 29858; Post Mortem, No. 5672.

Right upper: Electrocardiograms showing atrial fibrillation and low voltage.

Left upper: Aorta, stenosed, fibrosed mitral valve, and left atrium opened. The mural thrombi were lost in the dissection.

Left lower: The infarcted left kidney.

Right lower: The atheromatous aorta with the thrombus extending from 5 cm. above the bifurcation of the aorta into the common iliacs.

The heart weighed 600 grams (Fig. 3). There was an abundance of epicardial fat. The myocardium was dark, reddish-brown, and soft and flabby. The left atrium was dilated, its wall and endocardium were thickened, and thrombotic masses were present. All chambers of the heart contained numerous small, firm, whitish thrombi, attached to the endocardial surfaces. The left ventricular wall was 17 mm. thick; the right, 6 mm. The mitral valve leaflets were thickened and adherent to each other, causing moderate stenosis of the mitral orifice. These leaflets were about 0.5 mm. thick along their free edges. At the line of closure on the atrial surface the endocardium was eroded, and a very scanty amount of thrombus clung rather firmly to the small ulcerated area. Microscopic sections through this lesion showed that the vegetation consisted of fibrin and platelets, with scattered leucocytes, but no bacteria. The coronary ostia were slightly narrowed and not distensible. There was slight atherosclerosis of the coronary arteries, but no occlusion was seen.

The aorta showed a marked degree of atherosclerosis. The terminal 4 cm. of aorta contained a complete ring of calcareous deposits which extended slightly into the common iliacs. A thrombus beginning 2 cm. below the ostia of the renal arteries occluded the aorta beyond the bifurcation extending into the common iliacs and for a short distance into the external iliac arteries. In the aorta it was adherent posteriorly, and it was slightly retracted from the wall and free in the iliac vessels. The renal arteries, superior and inferior mesenteric arteries, and celiac axis were patent. The splenic artery was tortuous, had rigid walls, and contained a soft, dark red thrombus throughout its length.

The right lung weighed 550 grams. Along the posterior border of the upper lobe there were several hemorrhagic infarcts, the largest of which measured 4 cm. in its greatest dimension. Two smaller infarcts were seen on the lateral surface of the lower lobe. The left lung weighed 350 grams and appeared to be normal.

At the junction of the esophagus with the cardia, there was a small globular tumor mass in the muscle coat, measuring 7 mm. in diameter. Microscopically this proved to be a leiomyoma. Otherwise, the alimentary tract was normal. The liver weighed 2,100 grams. It showed a slight nutmeg appearance. Microscopically, passive congestion was evident, and, in addition, there were scattered, small areas of focal necrosis in the liver lobules. The gall bladder contained a spherical calculus 1 cm. in diameter. The pancreas showed a marked degree of fatty infiltration.

The spleen weighed 250 grams. At the upper pole it presented a large pale infarct.

The right kidney weighed 250 grams; the left, 170 grams. Both kidneys showed a moderate degree of nephrosclerosis of the benign type. Each kidney showed a few pale infarcts. The internal genitalia were absent. The brain weighed 1,250 grams. There were some small deposits of bony tissue in the dura mater along the sagittal sinus. There was atrophy of the frontal lobes of the cerebrum. Cross sectioning of the brain revealed considerable congestion of the white matter. The basal vessels of the brain showed moderate sclerosis.

CASE 4. *Rheumatic Mitral Stenosis, With Atrial Fibrillation, and Intermittent Claudication Due to a Saddle Embolus at the Bifurcation of the Aorta. Cerebral Embolism.*—Mrs. S. B., No. 68701, a 40-year-old Viennese refugee, had been diagnosed as having rheumatic mitral stenosis and insufficiency, with congestive failure, in 1938. She presented herself Aug. 20, 1941, complaining of a feeling of heaviness of the left leg, coolness, numbness, and tingling and yellow coloration of the feet, with purple toes on the dependent left foot. Two days previously, while walking about the house, she had had a sudden attack of pain in the calf of her left leg which radiated anteriorly. The left foot felt numb and was cold and blanched. She had some tingling sensation on the medial side of the foot. She went to bed and massaged the part, and soon the color reappeared, but the pain

persisted. Pallor returned two or three times, and each time friction would bring the color back. The foot continued to be cold and numb. After bathing the foot in warm salt water that night, the pain seemed to disappear. She got up and walked again, and after about a block she had the sharp pain in the right leg along the margin of the tibia into the foot. She again went to bed and the pain disappeared, but returned every time she tried to walk. One week preceding the pain in her left foot, she had had a cold with cough and fever, and had developed an irregularity of her heart.

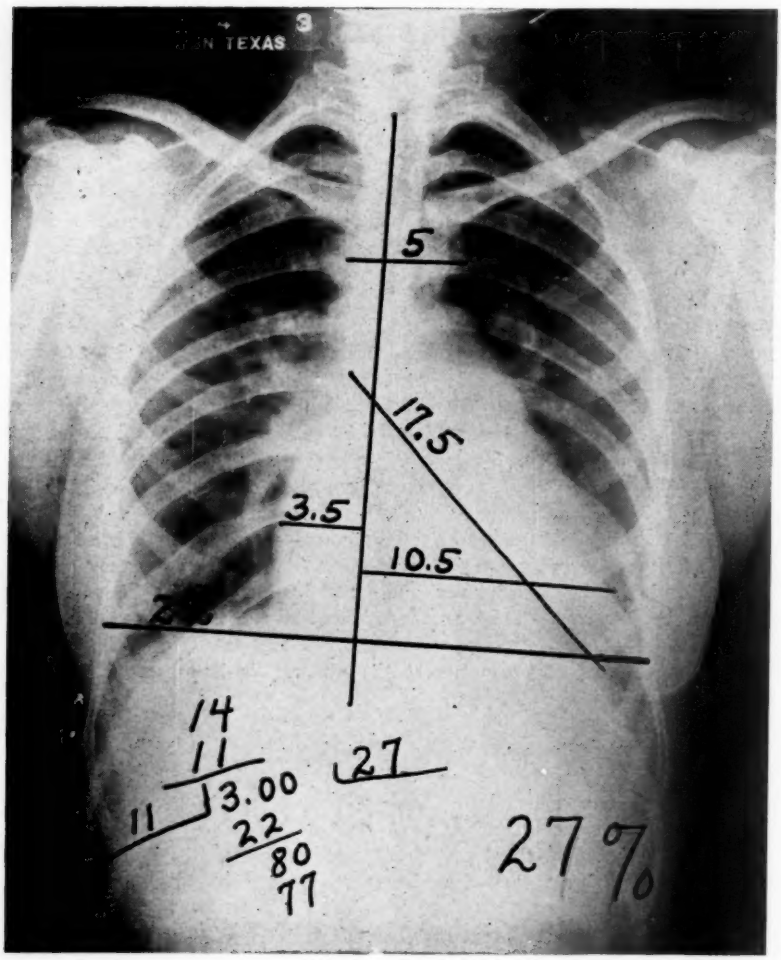
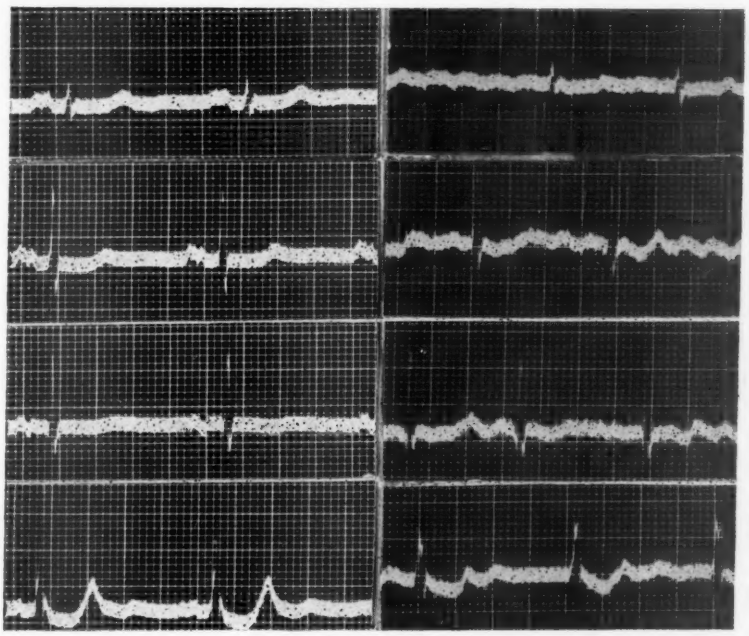


Fig. 4A.—Case 4. Mrs. S. B., J. S. Hospital, No. 68701. Teleroentgenogram showing the characteristic straight left ventricular border of rheumatic mitral stenosis.

Physical examination showed cyanosis and evidences of chronic rheumatic heart disease, with high-grade mitral stenosis. Her heart was enlarged. There were systolic and diastolic thrills over the apex and a diastolic pulmonary shock. The pulmonary second sound was accentuated. There were a loud apical systolic murmur, transmitted to the apex, and a short diastolic murmur. The first apical sound was sharp in spite of the murmur. The heart was somewhat overactive. The rate

was about 110. The rhythm was absolutely irregular. Electrocardiograms showed atrial fibrillation. The blood pressure was 160/100. There was some pulse deficit. The abdomen was protuberant. Examination of the lungs showed râles at the bases. The liver was 1 to 2 fingerbreadths below the right costal margin, and the spleen was palpable.

The extremities showed conspicuous abnormalities. The left foot was cooler than the right. The left big toe was slightly cyanotic and mottled. The dorsalis pedis, popliteal, and femoral pulsations could not be felt on the left, and were barely palpable on the right. There was slight tenderness in the calf of the left leg. The skin temperatures were reduced markedly on the left, and moderately over the right, leg. The oscillometric indices were practically zero in both the thighs and lower part of the legs.



Oct. 15, 1940. Jan. 9, 1942.

Fig. 4*B*.—Case 4. Electrocardiograms, from above downward, leads I, II, III, and IV, showing, Oct. 15, 1940, characteristic, broad, notched, diphasic P waves of atrial hypertrophy and tendency to right axis deviation; Jan. 9, 1942, atrial fibrillation.

The patient's course in the hospital was eventful. Paroxysmal attacks of pain recurred in the left leg, and then in the right leg. Cramping pains recurred in the lower abdomen and flanks, and were followed by general tenderness. The edge of the liver and spleen became palpable. She had dyspnea and precordial pain occasionally.

Antispasmodics, postural exercises, and pavaex therapy of the left leg were kept up, even though she had much pain in the leg after the exercises and after the intermittent negative pressure, but the skin of the left leg became warmer. She was discharged improved on Oct. 18, 1941.

She was readmitted Jan. 2, 1942 with an attack of abdominal pain, nausea, and vomiting that was followed by pains in her right leg, with the appearance of pallor and yellowness. The toes on the right foot began to feel peculiar, and a cold wave passed over the plantar surface of the right foot to the heel. Knifelike

pain radiated through to the sole of the right foot, and excruciating, gnawing, constant pain was felt in the right groin. Conspicuous pallor, hyperesthesia with coldness, and absence of peripheral pulses were noted in both legs. Oscillometric studies showed maximum indices of 1 in the right thigh, 1¼ in the left thigh, ¾ in the right leg, and 1 in the left leg. Abdominal cramps, nausea, and vomiting recurred. She had attacks of flushing, with burning of the face, neck, arms, and

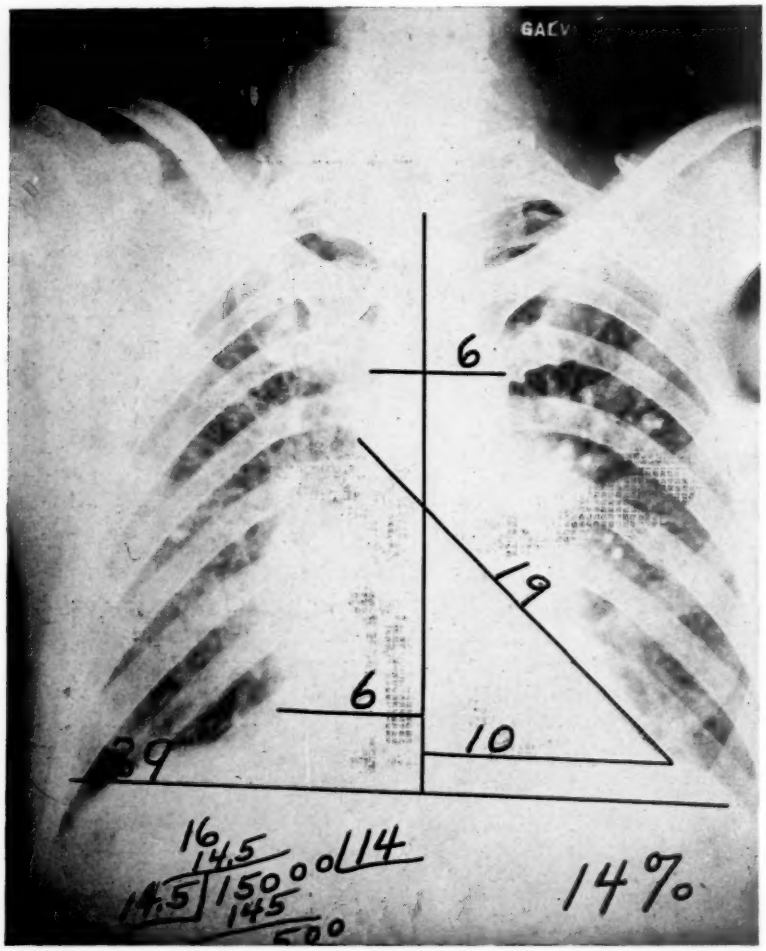
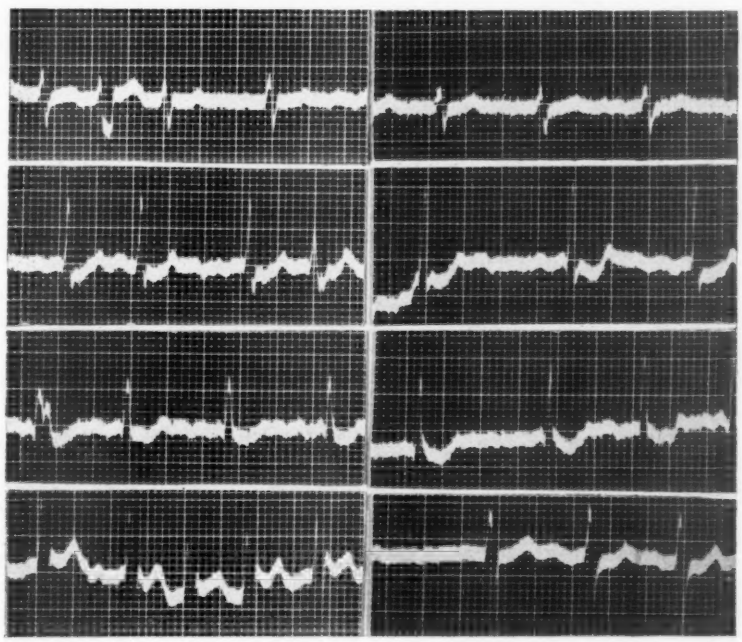


Fig. 5A.—Case 5. C. L. T., J. S. Hospital, No. 75690. Teleroentgenogram showing some bulging in the region of the left atrium, considerable bulging in the right atrium, and congestion in the lung typical of rheumatic mitral stenosis.

hands. The symptoms slowly decreased under conservative medical treatment with a heat cradle, postural exercises, and pavaex therapy. Some paresthesias persisted. On March 20, 1942, she had a syncopal attack, with respiratory standstill. She was partially revived by artificial respiration, but never became conscious again. Shortly before death she had Cheyne-Stokes respiration and the cold grayness of shock. No autopsy was done.

A diagnosis of saddle embolus at the bifurcation of the aorta and terminal cerebral embolism seemed warranted.

CASE 5. *Rheumatic Mitral Stenosis, With Chronic Atrial Fibrillation, Temporary Paraplegia, and a Saddle Embolus at the Bifurcation of the Aorta. Cerebral Embolism and Recovery.*—C. L. T., No. 75690, an insurance salesman, aged 48 years, had had rheumatic heart disease with atrial fibrillation for at least seven or eight years. Early in February, 1942, he contracted mumps, and developed orchitis, which sapped his strength. He stopped the daily use of digitalis which he had carried on for years. On April 2, 1942, he contracted an acute respiratory infection. During the night of April 7, he was awakened by agonizing pain which was sharp and localized behind the right knee. A few hours later he had a similar pain behind the left knee. Both legs became pale and felt very cold. He seemed paralyzed. He had fleeting pains in the abdomen and in the precordium.



April 29, 1942. May 18, 1942.

Fig. 5*B*.—Case 5. Electrocardiograms, from above downward, leads I, II, III, and IV F, showing right axis deviation and atrial fibrillation characteristic of advanced rheumatic heart disease.

Physical examination showed a high-grade, uncontrolled atrial fibrillation and the signs of cardiac dilatation and mitral disease. The heart rate was 144, and the blood pressure, 128/80. Marked pallor was noted in both legs, particularly when they were elevated. The skin temperatures were lowered above the knee. The skin of the right leg was cooler than that of the left, and the coolness extended slightly higher. The femoral pulse was not definitely palpable on the right and could barely be felt on the left. The popliteal, dorsalis pedis, and posterior tibial pulses could not be felt definitely on either side. The legs, particularly the right, blanched instantly when elevated and became flushed and slightly cyanosed when held dependent. The subsequent return of color when the legs were horizontal was slow.

The patient was treated with hot and cold applications, whiskey, passive movements, passive vascular exercises, and digitalis. He gradually regained ability to

move his legs, but continued to have attacks of sharp pain, particularly in the right leg.

On April 4, 1942, he was found lying in bed in a semicomatose state, mumbling incoherently; his face was drawn up to the right, and the right arm was limp. In a few days he regained control of the arm and the facial muscles, but he remained mentally confused. He was given 1,000 c.c. of saline by hypodermoclysis. The atrial fibrillation was brought under control with digitalis. His heart rate was reduced to 70. His mental condition gradually cleared under conservative treatment. The pains in the legs decreased and the skin became slightly warmer. He was gradually gotten up in a wheel chair and later allowed to use crutches. One month after his cerebral accident he was discharged much improved.

Diagnosis.—Rheumatic mitral stenosis, atrial fibrillation, saddle embolus at the bifurcation of the aorta, and cerebral embolism.

SUMMARY OF DATA AND CONCLUSIONS

The study of our five cases and of the literature emphasized several interesting clinical diagnostic points. Patients with coronary occlusion and myocardial infarction, and those with rheumatic mitral disease and auricular fibrillation or verrucous endocarditis are candidates for saddle embolism. The bifurcation of the aorta, iliacs, or other great arteries are not uncommon sites for the lodgment of relatively large emboli. The secondary aortic thromboses that follow in atheromatous aortae are most serious and fatal complicating processes.

The occurrence of abdominal cramps should lead one to suspect movement of the emboli down the aorta in predisposed patients. Such symptoms might well be considered significant and premonitory.

Sudden sharp pains in one leg and then in the other, followed by paresthesias, coldness, blanching, lowered skin temperatures, and absent or greatly decreased femoral pulses should lead one to suspect lodgment of an embolus at the bifurcation of the aorta. Oscillometric studies are confirmatory of the absence of pulsations.

The clinical pattern of saddle embolism has been quite clearly delineated. When the embolus is small and the obstruction incomplete, a much less dramatic and less clear-cut clinical picture is presented. It is surprising how benign the condition sometimes seems to be, even after a rather stormy beginning.

Papaverine hydrochloride in a dose of 0.032 Gm. (1/8 grain) intravenously should be started as soon after the onset as possible, and repeated as necessary. Morphine is used to control the pain. Whiskey should be administered freely. Passive movements, postural exercises, and pavaex therapy are to be undertaken. Lumbar sympathetic block should be produced as soon as possible to relieve pain and cause maximum peripheral vasodilatation.

In elderly persons the great likelihood of secondary thrombosis in an arteriosclerotic aorta must be kept in mind, and heparinization should be promptly instituted by the intravenous drip method.

Infarction of the kidneys, at times massive from retrograde aortic thrombosis, led to acute uremia in one of our cases. Intermittent

mesenteric obstruction apparently occurred also in the same case. Cerebral embolism may be a further complication.

The length of the time of survival after even complete obstruction and the long postponement of the development of, and the degree of, gangrene are often surprising.

Heparinization, followed by dicoumarol, may, someday, become a routine emergency procedure in the treatment in all cases of massive coronary thrombosis.

The patients with rheumatic heart disease seem to have the best prognosis insofar as saddle embolism is concerned.

Acute saddle embolism of the aorta following trauma in war is likely to occur. In young men this should have a favorable prognosis, especially if the condition is promptly recognized and treated with papaverine, heparin, and passive exercises. If embolectomy should be undertaken, it should be done by an expert vascular surgeon.

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ELECTROCARDIOGRAPHIC CHANGES DURING PNEUMOENCEPHALOGRAPHY

MALCOLM W. BICK, M.D., AND BERNARD S. EPSTEIN, M.D.
BROOKLYN, N. Y.

THE only reports on the electrocardiographic effects of pneumoencephalography are those of Abeles and Schneider,[1] who observed twenty cases, and Ambrosi,[2] who reported ten additional cases. Abeles and Schneider demonstrated changes in the pacemaking mechanism, including sinus bradycardia, sinus arrhythmia, nodal rhythm, phasic sinus slowing, ventricular extrasystoles, and auricular fibrillation. Ambrosi, who noted only a slight alteration in the heart rate, did not confirm these observations.

In view of this contradiction we believed it advisable to reinvestigate the problem. Theoretically, it seemed that electrocardiographic changes might be expected, inasmuch as the introduction of air into the cranial cavity results in central nervous system irritation. We endeavored to establish a more uniform technique than that employed by previous investigators. Twelve consecutive, unselected patients who were referred to the x-ray department for pneumoencephalograms were studied.

TECHNIQUE

Unless otherwise stated, the patients were prepared by the omission of lunch. One and one-half grains of phenobarbital were given an hour before, and $\frac{1}{75}$ grain of atropine sulfate, hypodermically, a half-hour before the encephalograms were made.

The electrodes were attached and left undisturbed throughout the procedure. After the patient was seated, about 2 c.c. of novocain were introduced into the subcutaneous tissues in the third or fourth lumbar interspace. The needle was inserted into the subarachnoid space, and the first tracing of the three classical leads was recorded before fluid was withdrawn.

Ten cubic centimeters were removed initially, and 5 c.c. of sterile, filtered oxygen were slowly introduced. During the rest of the procedure, equal quantities of fluid were removed and oxygen injected in 5 c.c. interchanges of fluid and gas. By this method sudden increases in the volume of gas in the subarachnoid space were avoided.

Twenty minutes to a half-hour were usually required. In some cases, the procedure was stopped momentarily to take tracings after small quantities of oxygen had been introduced. In all, a complete tracing was taken towards or at the end of the operation. In several instances, follow-up electrocardiograms were made.

Our technique differed from that used by previous investigators in the following details. We employed pure oxygen instead of air. A controlled fluid-gas ratio was maintained, and no wide differences between the amount of fluid removed and gas injected were permitted. The total amount of fluid removed averaged about 80 c.c., whereas the average quantity Abeles and Schneider removed averaged

From the Jewish Hospital of Brooklyn, Brooklyn, N. Y.
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about 200 c.c. In addition, careful records of the patients' reactions, including pulse rate, blood pressure, temperature, and subjective symptoms, were made before, immediately following, and at periodic intervals after the procedure.

Abeles and Schneider used morphine and scopolamine for premedication. Morphine alone, or in combination with other drugs, has been shown by Bohn[5] to provide less satisfactory premedication than the phenobarbital and atropine sulfate which we employed.

REPORT OF CASES

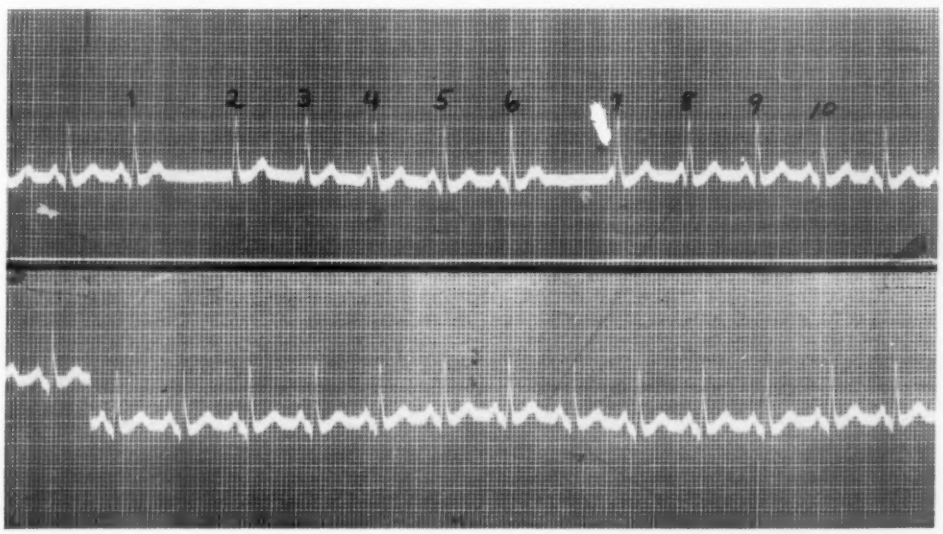
The cases are divided into three groups, according to the degree of alteration in the electrocardiogram. Three of the twelve patients showed marked changes, five showed moderate changes, and four showed only slight variations.

THE THREE CASES IN WHICH THERE WERE MARKED CHANGES

CASE 1.—E. S., a 38-year-old man, had had convulsive seizures and hesitancy of speech for five months. He began to transpose the position of words in sentences before admission.

The positive physical signs included blurring of the nasal margins of the optic discs, absence of the abdominal reflexes, equivocal Babinski and Oppenheim signs on the right side, and a questionable Hoffman sign on the left side. After the encephalograms were made he was discharged with a diagnosis of idiopathic seizures.

A.



B.

Fig. 1*A*.—Case 1. Lead II, after 20 c.c. of oxygen had been injected, shows dissociation of auricle and ventricle.

Fig. 1*B*.—Case 1. No irregularity in Lead II after the oxygen injection had been completed.

Before the introduction of oxygen, the electrocardiogram revealed a rate of 125 per minute with a slight tendency towards left axis deviation. After the introduction of 20 c.c. of oxygen the rate slowed to 100, and the pattern of the tracing was abruptly changed. The T wave in Cycle 1 (Fig. 1A) is notched and broadened, probably because a P wave is superimposed. Number 2 is a nodal beat because it is not preceded by a P wave. A P wave probably falls at the peak of

the following T wave. In Cycles 3 and 4 there is dissociation between the auricle and ventricle because the P-R intervals are 0.06 second and 0.08 second, respectively; P falls almost directly into the QRS complexes. Since it normally requires 0.12 second for an impulse to traverse the auricular tissue from the sinoauricular to the auriculoventricular node, we may assume that Cycle 5 shows return to the normal mechanism because P-R measures 0.12 second. In Cycle 6 the P-R interval of 0.14 second is normal.

The same sequence of events follows the main ventricular complex in Cycle 6, namely, a P wave is superimposed on the T wave and there are two nodal beats, followed by a return to normal mechanism. This phenomenon has been called "dissociation and interference" because both the sinoauricular node and the auriculoventricular node are operating independently.[4] When the sinus impulse arrives at the auriculoventricular node during a refractory period it fails to initiate a ventricular complex.

A tracing taken after the total amount of oxygen had been injected (Fig. 1B) and a follow-up tracing forty-eight hours later showed a slightly slower rate, but no essential variations from the preinjection record.

Comment.—This electrocardiogram showed a marked transient disturbance at the beginning of the injection, at the time of onset of severe headache. There were no progressive changes.

CASE 2.—J. C., a 22-year-old man, complained of seizures involving principally the right hand for the preceding five years. There had been no generalized convulsions and no loss of consciousness. The frequency and severity of the attacks were lessened by the use of phenobarbital. The patient had suffered a head injury at the age of 11 years. He remained in bed for three weeks at that time. When he was 16 years old he was injured by a truck, which struck his head. There were no immediate sequelae.

The positive signs included a rhythmical intention tremor on the right side, and right-sided hyperreflexia and facial weakness. Roentgenograms revealed hypertrophy of the skull bones on the left side. After the pneumoencephalograms were made, he was discharged with a diagnosis of hypoplasia or atrophy of the left cerebral hemisphere (traumatic or congenital).

The electrocardiograms showed many unusual features. The tracing made after insertion of the needle, before oxygen was injected, showed normal sinus rhythm with a rate of 106 per minute. After the injection of 74 c.c. of oxygen (Fig. 2), there was a fall in rate to 80, with marked sinus arrhythmia and many associated abnormalities.

In Lead I, after Cycles 1 and 2, marked slowing of the rate occurs. Cycle 3 is initiated by an abnormally low P wave and a short P-R interval, indicating that the impulse arose, not in the sinus node, but closer to the auriculoventricular node in the auricular musculature. Since the P-R interval in Cycle 3 is about 0.10 second, it is likely that the QRS complex is of nodal origin. Cycle 4 is introduced by an abnormally low, rounded P wave, followed by a normal main ventricular complex. However, the S-T segment, which is isoelectric elsewhere, is bowed upward. The T wave which follows is abnormally round and full. Directly after this T wave there are three flutter waves (rate, 300 per minute) which continue until normal mechanism supervenes in Cycle 5. The tracing from Cycles 4 to 5 may be interpreted as showing auricular flutter, starting in the abnormal P wave of Cycle 4.

In Lead II, marked sinus arrhythmia, with a wandering pacemaker, as manifested by an inverted and diphasic P wave in Cycles 2, 3, and 6, is evident. These occur during periods of marked slowing and indicate that ectopic auricular foci look over the pacemaking mechanism when the sinoauricular node became depressed.

In Lead III, Cycles 1, 2, 3, and 4 show "interference and dissociation" similar to that described in Case 1.

In addition to these disturbances in the conducting mechanism, there are also alterations in the height of the T waves in all leads. Slight alterations in the height of the P waves and a definite elevation in the S-T segment appear in Lead II. A tracing taken twenty-four hours later showed no essential variation from the one taken before the oxygen was introduced.

Comment.—This patient, who was well composed before the procedure, had severe objective and subjective reactions, including nausea, vomiting, sweating, severe headache, and syncope. The electrocardiographic disturbances, which were also very marked, indicated severe vagal depression of the sinus node, followed by a shifting pacemaker, auricular flutter, nodal rhythm, and P- and T-wave changes.

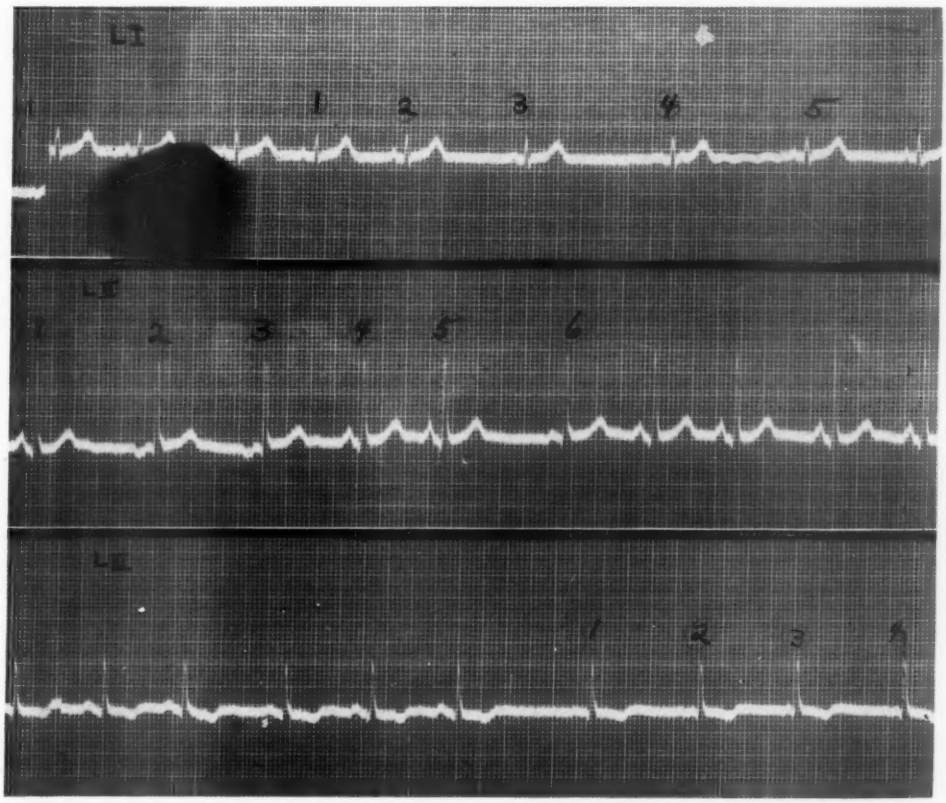


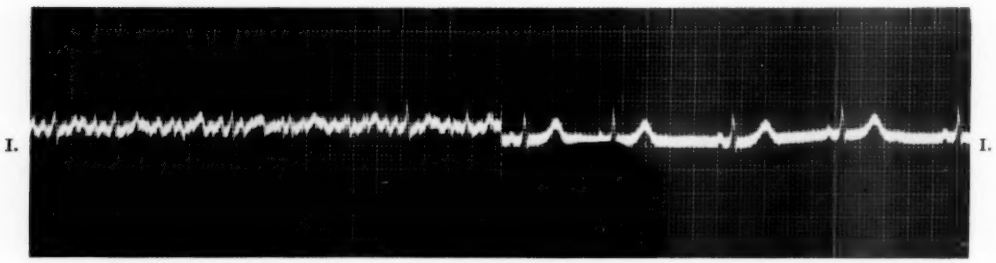
Fig. 2.—Case 2. After 74 c.c. of oxygen had been injected, all three leads show a disturbed pacemaking mechanism, with a wandering pacemaker, auricular flutter, nodal beats, and marked sinus arrhythmia.

CASE 3.—H. K., a 37-year-old woman, complained of numbness of the left hand and progressively severe tremor of the left hand and leg for two months. She had had "muscle weakness" of the left eye for eight years. The patient had had influenza in 1918.

The positive physical signs were atypical mask facies, failure of the left eye to converge, bilateral cogwheel rigidity, and continuous left-sided tremor involving the arm and leg. When she walked there were no associated left arm movements.

After the pneumoencephalograms were made, the patient was discharged with a diagnosis of postencephalitic Parkinson's disease.

The electrocardiographic changes were striking. Before the injection of oxygen the patient had a rapid regular heart rate of 130; a marked somatic tremor permitted us to identify only the main ventricular complexes. After the introduction of 20 c.c. of oxygen (Fig. 3A), there were slowing of the rate to 115 and a slight reduction in the tremor. After the total quantity of oxygen was injected (Fig. 3B), the heart rate fell to about 75, and sinus arrhythmia became evident. In addition, the somatic tremor entirely disappeared, and every portion of the record was clear. The tremor returned after a few hours, and the heart reached its usual rate of between 80 and 90 in twenty-four hours.

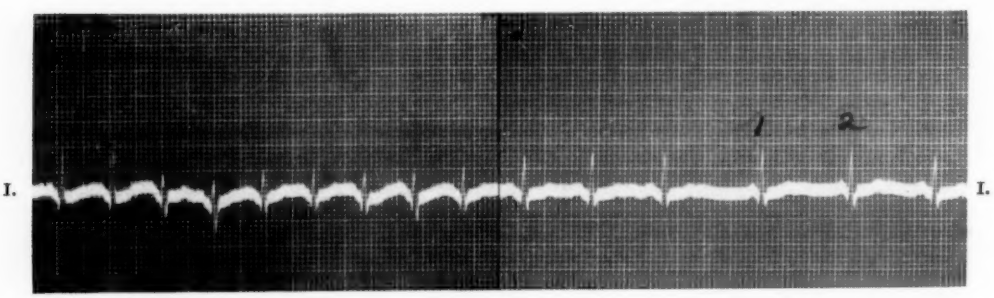


A. *B.*

Fig. 3*A*.—Case 3. After 20 c.c. of oxygen had been injected, marked somatic tremor persisted in this patient with Parkinson's disease. There is a rapid, regular rhythm.

Fig. 3*B*.—Case 3. After the injection of 110 c.c. of oxygen, the tremor disappears and sinus arrhythmia becomes apparent.

Comment.—The development of marked sinus arrhythmia and a bradycardia which persisted for many hours indicated a prolonged vagal effect. The patient had relief from her tremor for the only time since the beginning of her illness. One would not expect this to result from increased vagal activity because atropine or atropine-like drugs are most beneficial in Parkinson's disease. We know of no satisfactory explanation for this phenomenon. In this instance, too, moderately severe nausea and headache occurred at the same time as the electrocardiographic changes.



A. *B.*

Fig. 4*A*.—Case 4. Lead I, taken with the patient under general ether anesthesia, shows a rate of 160 per minute.

Fig. 4*B*.—Case 4. After 60 c.c. of oxygen, the heart slows to 110. Sinus arrhythmia and a disturbed pacemaking mechanism are observed. The P-R interval in Cycles 1 and 2 is abnormally short.

THE FIVE CASES IN WHICH THERE WERE MODERATE CHANGES

CASE 4.—T. K., a 9-year-old boy, had had momentary seizures involving the right hand during the preceding eighteen months. Two days before admission the patient had two severe jacksonian seizures.

Physical and laboratory examination showed nothing abnormal.

After encephalograms had been made, the patient was discharged with a diagnosis of idiopathic epilepsy. Pneumoencephalograms were made under general ether anesthesia. The premedication consisted of one grain of phenobarbital the night before, 1½ grains of nembutal two hours before, and $\frac{1}{100}$ grain of atropine sulfate three-quarters of an hour before the procedure.

The electrocardiogram, which was taken after the patient was well anesthetized, and with the needle in situ, revealed a sinus tachycardia of 160; fusion of the P and T waves made most measurements inaccurate. There was marked cyclic alteration in the height and direction of the main ventricular complexes, probably a respiratory effect (Fig. 4A).

After the injection of 6 c.c. of oxygen (Fig. 4B), the rate slowed to 110, and the individual waves could be measured readily. The QRS complexes were taller and did not vary as much in height or direction as in the initial tracing. There was moderate sinus arrhythmia. The P-R intervals in Cycles 1 and 2 in Lead I shorten from 0.14 second to 0.10 second, indicating a wandering pacemaker. A tracing taken seventy-two hours later showed slowing of the heart rate to 80, with slight sinus arrhythmia.

Comment.—Despite general anesthesia and lack of subjective reactions, evidence of vagal stimulation was present in the electrocardiogram.

CASE 5.—J. H., a 55-year-old man, entered with a complaint of dizzy spells for three years and syncopal attacks which had become more severe during the preceding six months.

Examination revealed sclerotic peripheral vessels and questionable pallor of the left optic disc. After pneumoencephalograms had been made, the patient was discharged with a diagnosis of cerebral arteriosclerosis.

A tracing taken two days before the encephalograms were made showed normal sinus rhythm and a rate of 75 per minute. There was left axis deviation, and the T wave was inverted in Lead III. Because of technical difficulties we were unable to obtain a satisfactory tracing immediately before the injection of oxygen. The record made after the injection of 20 c.c. of oxygen showed several changes. The rhythm was normal and the rate was 110 per minute. There was an increase in voltage, particularly in Lead II. In Lead III, the change of the T wave from an inverted to an upright position is unusual. The P waves and T waves in the other leads were higher. In the record taken immediately after the injection of 70 c.c. of oxygen, the T waves had returned to the inverted position and the record resembled more closely the two control tracings. The increased voltage persisted and the P and T waves were elevated, but not as markedly as in the tracing taken after only 20 c.c. had been injected.

Comment.—The most marked electrocardiographic changes occurred early in the procedure, as in Case 1. They were accompanied by a transient period of retching and the onset of headache.

CASE 6.—A. B., a 14-year-old-boy, had had seizures in the right arm for three years. The past history was significant in that the patient was born by breech extraction and had had convulsions early in infancy. At the age of 6 years, he was hit by an automobile and was unconscious for five days.

On examination he showed mental retardation and atrophy of the right lower extremity. The right leg was shorter and smaller than the left. There was marked right-sided hyperreflexia.

Electrocardiographic studies before the injection of oxygen (Fig. 5A) showed sinus tachycardia (125 per minute). A tracing taken after 45 c.c. of oxygen had been injected (Fig. 5B), showed slight reduction in rate (to 110), with definite elevation of the T waves in all leads, including Lead III, in which the T waves were inverted. In addition, the S-T segments in Leads I and II were somewhat depressed. There was also deepening of the S wave in Lead II. In Lead III the P waves were considerably reduced in size.

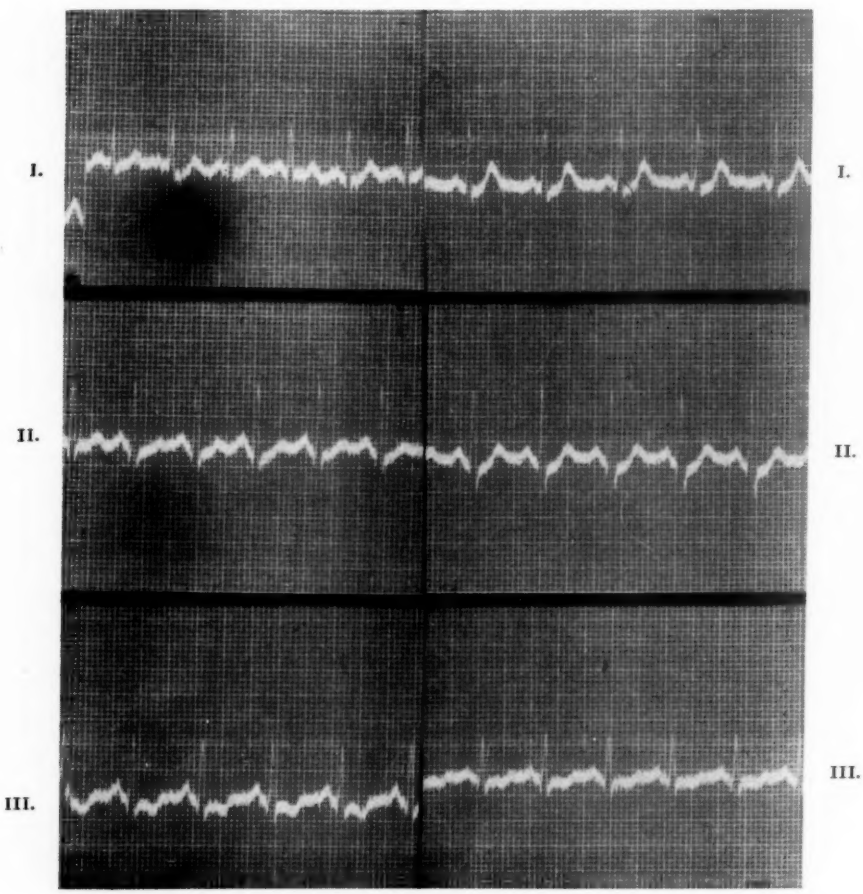


Fig. 5*A*.—Case 6. Before the injection of oxygen.

Fig. 5*B*.—Case 6. After 45 c.c. of oxygen had been injected. Elevation of T waves and depression of P waves in all leads, together with an insignificant decrease in rate.

Comment.—This case demonstrated primarily a change in the P and T waves, with no appreciable alteration in the pacemaker. These changes may have been caused by increased vagal activity.

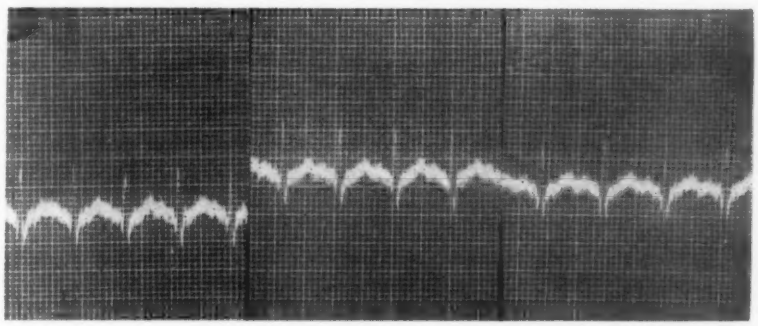
CASE 7.—S. M., an 8-year-old boy, entered the hospital because of dizziness and frontal headache for six months. During an attack he developed pain and a limp in the left leg. Four years previously he had been injured in an automobile accident. A diagnosis of concussion of the brain had been made at that time.

Examination showed a talkative, excitable child. Nystagmus of a congenital nature was present. There were girdle adiposity and a healed right mastoid scar, but no localizing neurologic signs. The patient was discharged with a diagnosis of a right cerebral scar and mild mental deficiency.

Pneumoencephalograms were made under general ether anesthesia.

The electrocardiogram showed normal sinus rhythm, and a rate of 100 before oxygen injection. After the introduction of 80 c.c. of oxygen the rate increased to 110, accompanied by an increase in voltage. In all leads the S-T segment became longer, and the upstroke of the T wave in Leads I and III was more gradual, with an earlier take-off. The T wave in Lead III, which was barely inverted in the initial tracing, was definitely deepened and inverted in the post-operative tracing.

Comment.—This is another case in which the changes were primarily confined to the configuration of the T waves and the S-T segments.



A. *B.* *C.*

Fig. 6*A*.—Case 9. Rapid, regular rhythm before the introduction of oxygen.
Fig. 6*B*.—Case 9. After injection of 20 c.c. of oxygen.
Fig. 6*C*.—Case 9. Only slight slowing after injection of 75 c.c. of oxygen.

CASE 8.—P. F., a 43-year-old woman, was admitted because of difficulty in walking, weakness of the legs, and frontal headaches for about one year. Shortly before, personality changes, surliness, carelessness, and poor memory had become apparent.

On examination the patient manifested frequent mood changes, poor memory for recent events, a positive Babinski on the left, and slightly slurred speech.

Three days after pneumoencephalograms were made, a right frontal craniotomy was performed and a large portion of a glioblastoma multiforme was removed. The patient expired four days after operation.

A tracing before insertion of the needle was identical with that taken after the needle had been inserted. After 20 c.c. of oxygen were injected, the rate increased from 80 to 100 per minute. Although the patient held herself tensely, a satisfactory second lead tracing was obtained; it showed elevation of the P wave from 3 to 5 mm., with a sharp upstroke and peak. After the injection of 75 c.c. of oxygen, an increase of the P waves in all leads persisted, and moderate elevation of all the T waves appeared. A record taken seventy-two hours later showed little variation from the preoperative control tracing.

Comment.—The patient cooperated very well in the early part of the procedure, but then became very excited, restless, and somewhat irrational. This explains the fact that there was an increase, rather than a decrease in heart rate. It is interesting that, despite this, there were T-wave changes similar in character to those in records in which the heart rate was diminished.

TABLE

CASE	DIAGNOSIS	EKG CHANGES	IMMEDIATE REACTIONS	DELAYED REACTIONS	BLOOD	
					BASAL	P.O.
No. 1 male, 38 E. S.	Convulsive seizures, idiopathic	Rate slows, nodal beats, dissociation and interference of SA and AV nodes	Headache	Backache 1 day, headache 4 days	140/90	130/90
No. 2 male, 22 J. C.	Hypoplasia, left cerebral hemisphere	Rate slows, nodal beats, auricular flutter, sinus arrhythmia, wandering pacemaker, S-T and T-wave elevation	Headache, sweating, pallor, vomiting, syncope	Chills 1 hour, headache 12 hours, backache 24 hours	140/96	138/65
No. 3 female, 37 H. K.	Postencephalitic Parkinsonism	Rate slows, sinus arrhythmia, disappearance of somatic tremor	Headache, nausea, vomiting	Nausea 24 hours, headache 48 hours	112/70	100/70
No. 4 male, 9 T. K.	Jacksonian seizures, origin undetermined	Rate slows, sinus arrhythmia, wandering pacemaker, increased voltage	None: patient under general anesthesia	Headache 48 hours, backache 48 hours		110/70
No. 5 male, 55 J. H.	Cerebral arteriosclerosis	Rate slows, increased voltage, P and T waves elevated	Headache, nausea, retching	Headache 18 hours	116/80	120/80
No. 6 male, 14 A. B.	Birth injury, left motor cortex	Rate slows, T-wave elevation, S-T segment depression, P-wave depression	Headache	Chills 1 hour, backache 36 hours, headache 48 hours	110/60	90/55
No. 7 male, 8 S. M.	Cerebral scar, right	Rate accelerates, T-wave and S-T segments alterations	None: patient under general anesthesia	Pain in ears 12 hours		120/90
No. 8 female, 43 P. F.	Glioblastoma multiforme, right frontal area	Rate accelerates, P- and T-wave elevation	Headache, nausea	Restless 48 hours, headache 72 hours	116/70	110/70
No. 9 male, 37 N. G.	Headache due to conversion hysteria	Rate slows slightly, less tendency to left axis deviation	Headache, nausea, retching	Headache 25 hours, backache 24 hours	130/98	120/90
No. 10 male, 30 J. C.	Posteoncussion syndrome	Rate slows slightly, slight T-wave elevation	Severe headache	Headache 48 hours	138/84	110/75
No. 11 female, 26 F. R.	Idiopathic convulsive disorder	Rate slows slightly, minimal T-wave and S-T segment elevation	Headache, nausea, retching	Chills 15 min., dizziness 24 hours, headache 4 days	100/70	100/70
No. 12 male, 38 E. D.	Cerebral arteriosclerosis	Rate slows slightly	Headache, sweating	Chills 12 hours, headache 24 hours	140/90	160/130

THE FOUR CASES IN WHICH THERE WERE SLIGHT CHANGES

CASE 9.—N. G., a 37-year-old man, complained of headache for four months, accompanied by faulty memory. Many years before, the patient had had "spastic colitis." The patient was emotionally upset.

Examination revealed an agitated normal man with hyperactive deep reflexes, absent abdominal reflexes, and a slightly enlarged prostate. He showed evidences

I

PRESSURE		PULSE				TEMPERATURE				LUMBAR PUNCTURE MM. H_2O		SPINAL FLUID C.C. REMOVED	OXYGEN C.C. INJECTED
4 HR.	24 HR.	BASAL	P.O.	4 HR.	24 HR.	BASAL	P.O.	4 HR.	24 HR.	IMMEDIATE PRESSURE	FINAL PRESSURE		
150/100	130/100	80 to 90	80	120	80	98 to 99	98.6	101.2	98.6	185	115	90	80
130/80	140/98	70 to 90	74	90	84	98 to 100	98.6	101	99	290	275	77	74
	86/72	80 to 90	68	72	88	98.6 to 100	98.6	99.8	100	130	70	115	110
112/70		70 to 80	80	116	88	97 to 99.2	98	99.2	99.2	---	---	70	60
130/80	124/80	60 to 80	70	90	72	98 to 99.2	99.4	100.8	99.8	140	125	75	70
110/60	114/64	80 to 90	72	80	80	98 to 99	99	100.6	98.6	180	120	63	61
105/75		88 to 100	92	120	88	98 to 100	97.8	101	98.6	---	---	85	80
140/90	110/70	70 to 90	100	64	80	98 to 99.9	98.6	100	98.6	170	90	80	75
140/80	124/88	75 to 120	118	100	118	99 to 99.8	99.2	100.4	99.8	170	95	80	75
120/74	126/76	80 to 90	102	90	90	98 to 99.6	100	100.2	99	180	130	45	40
105/80	90/60	70 to 90	92	90	90	98 to 99	97.4	100	99.2	120	68	80	75
150/110	150/130	70 to 90	120	120	90	98 to 100	99	100	99	110	60	76	75

of vasomotor instability. After pneumoencephalograms had been made, the patient was discharged with a diagnosis of headache caused by conversion hysteria.

The electrocardiographic changes were minimal. A sinus tachycardia of 165 in the initial tracing (Fig. 6A) slowed to 150 after the introduction of 20 c.c. of oxygen (Fig. 6B), and to 135 after 75 c.c. of oxygen were injected (Fig. 6C). The individual waves cannot be well differentiated. In the initial record there was a tendency to left axis deviation. This was diminished in the final tracing.

Comment.—This patient was extremely anxious prior to the procedure. Sympathetic hyperactivity was reflected in the record, which showed only slight slowing and minimal modification during encephalography. He suffered from nausea, retching, and headache, but there was little correlation between these symptoms and the minimal electrocardiographic changes.

CASE 10.—J. C., a 30-year-old man, was admitted to the hospital because of dizziness and headache for one year following a fall. Examination revealed a markedly apprehensive man with a scar over the right temple and tenderness over the lumbar spine.

After encephalograms had been made he was discharged with a diagnosis of postconcussion syndrome.

The electrocardiographic changes were minimal. A tracing, taken after the injection of 10 c.c. of oxygen, revealed no alteration in the tachycardia (140) which was present before the injection. The final tracing, taken after the injection of 40 c.c. of oxygen, showed only slight slowing of the rate (to 130). Lead II, taken after 10 c.c. had been injected, showed slight elevation of the T waves which was not present in the final record.

Comment.—Only 40 c.c. of oxygen were injected. This might account for the slight electrocardiographic changes. It is doubtful, however, whether a larger quantity of oxygen would have caused further changes, because the most marked alterations occurred at the beginning of the injection. This patient was extremely apprehensive. Fear prevented any appreciable alteration in either rate, rhythm, or configuration by producing increased sympathetic activity.

CASE 11.—F. R., a 26-year-old woman, had had convulsive seizures in the left foot two or three times a year for thirteen years, followed by spread to the left arm and right leg. For seven months she had had daily occipital and frontal headaches. The patient had had heart disease since birth.

Examination revealed a pale, thin, apprehensive, cyanotic woman with loud systolic murmurs, an enlarged heart, clubbing of the fingers, and bilateral pes cavus.

The electrocardiographic changes were insignificant. A slight slowing of the rate (from 130, initially, to 110 at the end of the procedure) was observed. A very slight elevation of the T waves and S-T segments appeared in Leads II and III after 25 c.c. of the gas had been injected. Marked right axis deviation and abnormally large P waves in Leads II and III were present in all the tracings. These were ascribed to the congenital cardiac defect.

Comment.—Again, the only measurable changes occurred early in the procedure. Her extreme anxiety was responsible for the initial and persistent tachycardia. No correlation existed between the minimal electrocardiographic changes and the moderately severe retching, nausea, and vomiting.

CASE 12.—E. D., a 38-year-old man, had a severe dizzy spell three weeks before admission. Three years previously he had had a transient hemiplegia which cleared completely within forty-eight hours.

Examination revealed mental retardation, retinal arteriosclerosis, and mild hypertension. The pneumoencephalogram showed definite dilatation of the sulci, and he was discharged with a diagnosis of encephalomalacia secondary to arteriosclerosis.

The electrocardiograms showed little alteration. An initial tachycardia of 140 slowed to 130 at the end of the procedure. Low voltage was present in all leads in the preoperative tracings, as well as in those taken during and after the procedure. Very slight elevation of the T wave in Lead II was observed after the injection of 50 c.c. of oxygen.

Comment.—This man was worried for two days before the encephalograms were made. Other than headache, there were no symptoms. The tachycardia was a reflection of his anxiety. The minimal alterations in the electrocardiogram may have been caused by sympathetic overactivity.

DISCUSSION

In eight of our twelve cases, appreciable electrocardiographic changes occurred during pneumoencephalography. Abeles and Schneider reported an incidence of 75 per cent in their twenty cases. Our observations do not confirm those of Ambrosi, who reported only slight alterations in the heart rate. We found alterations which varied in type and degree in all our cases. They can be divided into two general categories: those concerned with the pacemaking mechanism, and those which, for lack of a better name, may be called wave changes. Both types may occur in the same patient.

In ten cases in the first group there were changes which varied from a slight slowing of rate to sinus arrhythmias, nodal beats, auriculoventricular dissociation and interference, wandering pacemaker, and auricular flutter.

In eight cases in the second group there were slight to marked alterations in the P and T waves and the S-T segments. Variations in the height and direction of the QRS complexes occurred in two cases. These two types of alterations have no direct relationship to each other. In some cases only slight wave changes appeared when there was a marked pacemaker disturbance. In other cases the converse was true.

The electrocardiographic changes in several cases were most marked at the beginning of the procedure. In others, the changes began immediately upon the introduction of the gas and progressed throughout the procedure. The changes in the pacemaking mechanism were caused by vagal activity. The rapidity with which these alterations were initiated suggested a central mechanism. It is possible that the wave changes also were of vagal origin.

The electrocardiographic changes could not be correlated with the other side reactions in degree. Nausea, headache, and similar complaints commenced at the same time as the electrocardiographic alterations. In three patients with minimal electrocardiographic changes there were severe subjective symptoms (Cases 9, 11, and 12). Two other patients with marked or moderate electrocardiographic variations had minimal symptoms (Cases 1 and 6). From this lack of correlation one may conclude that the introduction of oxygen into the subarachnoid space stimulates several centers simultaneously, but not to the same extent. It is our belief that the cardiac changes are caused principally by central vagal stimulation, whereas the other side-reactions are, for the most part, brought about in other ways.

Vagal stimulation in itself may be responsible for side-effects. In the only case in which syncope occurred, evidence of more powerful vagal

stimulation was found in the electrocardiogram than in any other tracing. There can be little doubt that, in this instance, the central vagal mechanism was responsible for the collapse. The syncope in this case was different from the reflex vasovagal or vagovagal type, in that the stimulation reached the central nervous system directly.

In those cases in which the changes were minimal, the patients were most apprehensive and excitable, and showed marked tachycardia. The dose of $\frac{1}{75}$ grain of atropine, which was given before making the encephalograms, was well below that required to cause alteration in the heart rate.[3] It is reasonable to assume, therefore, that in these instances the psychic disturbance caused a marked sympathetic outflow which prevented any abnormal vagal stimulation from altering the pacemaker mechanism or initiating conductive changes in the heart itself. It would follow, then, that larger doses of atropine might be used for the normal adult as routine premedication. In addition, it would seem advisable to reinforce this with one of the sympathicomimetic drugs.

SUMMARY

Electrocardiographic changes indicative of increased vagal activity occur during encephalography.

The authors wish to express their thanks to Dr. L. M. Davidoff and Dr. M. G. Wasch for their cooperation and interest.

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STUDIES OF THE VARIATION IN CIRCULATORY AND RESPIRATORY RESPONSES TO CAROTID SINUS STIMULATION IN MAN

MORTON GALDSTON, M.D., ROBERT GOLDSTEIN, M.D., BALTIMORE, MD., AND J. MURRAY STEELE, M.D., NEW YORK, N. Y.

IT IS now nearly a century and a half since Parry[1] noticed that pressure on the neck along the course of the carotid arteries might cause slowing of the heart, but only lately has the nature of the mechanism become clear. Prior to recent work it was generally regarded as due to stimulation of the vagus nerve,[2, 3] and came to be known as "Vagusdruckversuch" or "vagus pressure test." In 1900, Pagano[4] and Siciliano[5] showed, however, that although the cardiac slowing was mediated through the vagus, it was primarily dependent upon a reflex from the carotid arteries, and Sollmann and Brown,[6] in 1912, clearly demonstrated that traction on the carotid arteries in the absence of stimulation of the vagus nerve produced a fall in arterial pressure as well as slowing of the heart. Hering's[7, 8, 9] painstaking physiologic and anatomic studies (1923 to 1927) on the pathways of the nervous impulses first served to bring general recognition to the reflex nature of the phenomenon. Through the work of Hering's associate, Koch,[10, 11] and Heymans and his co-workers,[12, 13, 14] De Castro,[15] and Sunder-Plassmann,[16] a clearer definition of the mechanism of the carotid sinus and its pathways came about.

In 1933 and 1935, Weiss and Baker[17] and Ferris, Capps, and Weiss[18] reported instances of syncope and convulsions in persons in whom it was easy to reproduce attacks by slight pressure upon the carotid sinus. Hering[8] had suggested that such a response might account for certain instances of syncope and convulsions in man. Weiss and his co-workers distinguished three types of syncope as a result of carotid sinus stimulation. Usually two or more varieties occurred simultaneously. The first, in which syncope was accompanied by marked slowing of the heart rate or asystole, and a consequent fall in arterial pressure, was designated the "vagal type;" the second, in which a marked fall in arterial pressure occurred without significant slowing of the heart, the "depressor type"; and the third, in which there was syncope without either slowing of the heart or fall in arterial pressure, the "cerebral type." A response similar to the "cerebral type" was reported at about the same time by Danielopolu,[19] who believed that hypersensitivity of the

From the Department of Medicine, New York University College of Medicine, and the Third (New York University) Medical Division, Goldwater Memorial Hospital, Welfare Island, New York.

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TABLE I

CIRCULATORY CHANGES IN PATIENTS WITH CAROTID SINUS SYNCOPE

CASE	AGE	ARTERIAL PRESSURE		PULSE RATE		TYPE OF RESPONSE			SYNCOPE AND/OR CONVULSIONS	DIAGNOSIS
		RESTING	DURING STIM.	RESTING	DURING STIM.	V*	D*	C*		
1. J. M.	53	R 240-250/100	130/60	90	5-7 sec. asystole	+	-	-	yes	General arteriosclerosis, arterial hypertension
		L 240-250/100	150/60	90	36	+	-	-	no	
2. A. M.	46	R 170/90	120/60	84	5½ sec. asystole	+	-	-	yes	Cirrhosis of liver
		L Arterial tracing not obtained								
3. R. P.	50	R 170/100	90/50	96	36 with 3 sec. asystole	+	-	-	yes	Pulmonary tuberculosis postoperative bilateral lumbar sympathectomy for frostbite of both feet
		L 150/90	110/60	80	48	+	+	-	no	
4. E. B.	55	R 210-220/100-110	95/40	108	24	+	+	-	yes	Tabes dorsalis, arterial hypertension
		L 210-220/100-110	110/55	108	40	+	+	-	no	
5. J. K.	56	R 180/90	100/50	60	7 sec. asystole	+	+	?	yes	Arterial hypertension, general arteriosclerosis, right hemiplegia
		L 180/90	100/50	60	14 sec. asystole	+	+	-	yes	

All patients listed are males.

*V—vagal, D—depressor, C—cerebral.

6 C. K.	69	R 180-190/90	70/40	60	10-13 sec. asystole	+	+	-	yes	General arteriosclerosis. Parkinson's syndrome, arterial hypertension
		L 180-190/90	70/40	60	13 sec. asystole	+	+	-	yes	
7. A. S.	60	R 220/110	140/70	68	48	+	+	-	yes	Tabes dorsalis, arterial hypertension
		L 220/110	160/80	68	60	+	+	-	no	
8. W. B.	77	R 210-220/110	110/50	82	32 with 5 sec. asystole	+	+	-	no	General arteriosclerosis, pulmonary fibrosis and emphysema, arterial hypertension
		L 210-220/110	100/50	82	10-15 sec. asystole	+	+	-	yes	
9. F. H.	77	R 150/75	100/50	84	5 sec. asystole	+	+	-	yes	General arteriosclerosis, arteriosclerotic heart disease, cirrhosis of liver
		L 150/75	100/50	84	36	+	+	-	no	
10. C. M.	57	R 190/100-110	110-130/60	72	36	+	+	-	no	Subacute combined sclerosis, pernicious anemia, arterial hypertension
		L 190/110	120/70	80	48 with 3 sec. asystole	+	+	-	yes	
11. J. F.	70	R 170/80	110/50	72	6 sec. asystole	+	+	-	yes	General arteriosclerosis, right hemiplegia
		L 150/80	130/70	60	48	+	+	-	no	
12.† E. D.	52	R 160/100	90/50	90	10 sec. asystole	+	+	-	yes	General arteriosclerosis, arterial hypertension, thrombosis left common, external and internal carotid arteries

†Cases 12, 14. Thrombosed left carotid arteries were surgically removed prior to the study. There was no hypersensitivity of the carotid sinus of this side[55].

TABLE I—CONT'D

CASE	AGE	ARTERIAL PRESSURE		PULSE RATE		TYPE OF RESPONSE			SYNCOPE AND/OR CONVULSIONS	DIAGNOSIS
		RESTING	DURING STIM.	RESTING	DURING STIM.	V*	D*	C*		
13. O. C.	69	R 230-240/100-110	170/60	90	13	+	+	+	yes	Meningovascular syphilis, arterial hypertension
		L 230-240/100-110	150/70	90	60	+	+	+	yes	
14.† R. S.	51	R 300/140	180/75	96	36	+	+	+	yes	Arterial hypertension, general arteriosclerosis, thrombosis left common, internal and external carotid arteries
15. G. K.	65	R 120/70	80/50	66	48	+	+	-	no	General arteriosclerosis
		L 120/70	80/50	72	48	+	+	+	yes	
16. J. L.	70	R 200/90	110/50	102	62 with 3 sec. asystole	+	+	-	no	Arterial hypertension, general arteriosclerosis, right hemiplegia
		L 200/90	180/80	102	84	+	+	+	yes	
17. C. N.	53	R 260/110	190/100	96	36	+	+	-	no	Meningovascular syphilis, arterial hypertension, general arteriosclerosis
		L 260/110	260/110	96	96	-	-	+	yes	

carotid sinus played an important role in the cause of convulsions in epileptics.

Because of the difficulty in following changes in arterial pressure and pulse rate continuously by the usual technique during the brief period in which the reactions caused by pressure upon the carotid sinus occur, the existence of the so-called cerebral type has been in doubt. Since methods of recording arterial pressure and pulse rate continuously by direct intra-arterial measurements have recently become available,[20, 21] a restudy of the relationships, in point of time, between changes in arterial pressure, pulse rate, venous pressure, respiration, and the onset of syncope and convulsions was believed warranted.

One hundred persons were examined, twenty-six of whom had a sensitive carotid sinus reflex, in the sense that syncope and convulsions, with or without circulatory changes, occurred promptly with gentle pressure. Of these, seventeen regularly had convulsive seizures on stimulation of the carotid sinus. All of them were men whose ages ranged from 46 to 77 years (Table I). Four women and five men were not sufficiently cooperative for detailed study. Three patients (Cases 11, 12, and 15) gave a history of having experienced spontaneous attacks similar to those produced by pressure on the carotid sinus.

METHODS

The patient was placed in the supine position on a comfortable stretcher, with the arm to be used for arterial puncture extended on a padded board support at an angle of about 70° or 80° to the longitudinal axis of the body. The radial artery was located and the skin and subcutaneous tissues about the site were injected with approximately 0.5 c.c. of 2 per cent novocain solution. A sharp, short-beveled, 20-gauge Luer needle, connected by lead tubing to a Hamilton manometer, was inserted. Only occasionally was any marked discomfort experienced by the subject. Venous pressure was recorded through a 20-gauge needle inserted in the antecubital vein and connected with a second Hamilton manometer barrel fitted with a rubber membrane. Respiration was recorded by transmitting the pressure changes in a rubber bag, inflated with air to a pressure of 2 to 3 mm. Hg, inside of a linen binder placed loosely about the chest, to a third Hamilton manometer barrel fitted with a rubber membrane. The beginning and end of carotid sinus stimulation and of syncope and convulsions were recorded by passing a card in front of the camera. Drugs, such as atropine sulfate and paredrine hydrobromide,* were given intravenously, and the beginning and end of the injection were recorded.

Stimulation of the carotid sinus was carried out digitally. Occasionally, in sensitive persons, the palpation necessary to locate the sinus caused mild stimulation. Pressure on the sinus was often gentle, sometimes firm, but in no case was it sufficient to shut off the arterial supply, as evidenced by the fact that pulsation could be felt above the site of pressure. Even though the artery may have been partially occluded in rare instances, the observed effects on pulse rate and arterial pressure were not attributable to partial closure of the artery, for complete closure could be carried out either above or below the site of the carotid sinus without their occurrence. Pressure below the sinus sufficient to reduce pressure within it regularly called forth a mild rise of arterial pressure and pulse rate.

*Paredrine hydrobromide for these studies was kindly supplied by Smith, Kline & French Laboratories.

CIRCULATORY RESPONSES

The response to digital pressure upon the carotid sinus was recorded in each instance before and after the intravenous injection of 2.5 mg. of atropine sulfate and, at some other time, before and after 10 mg. of

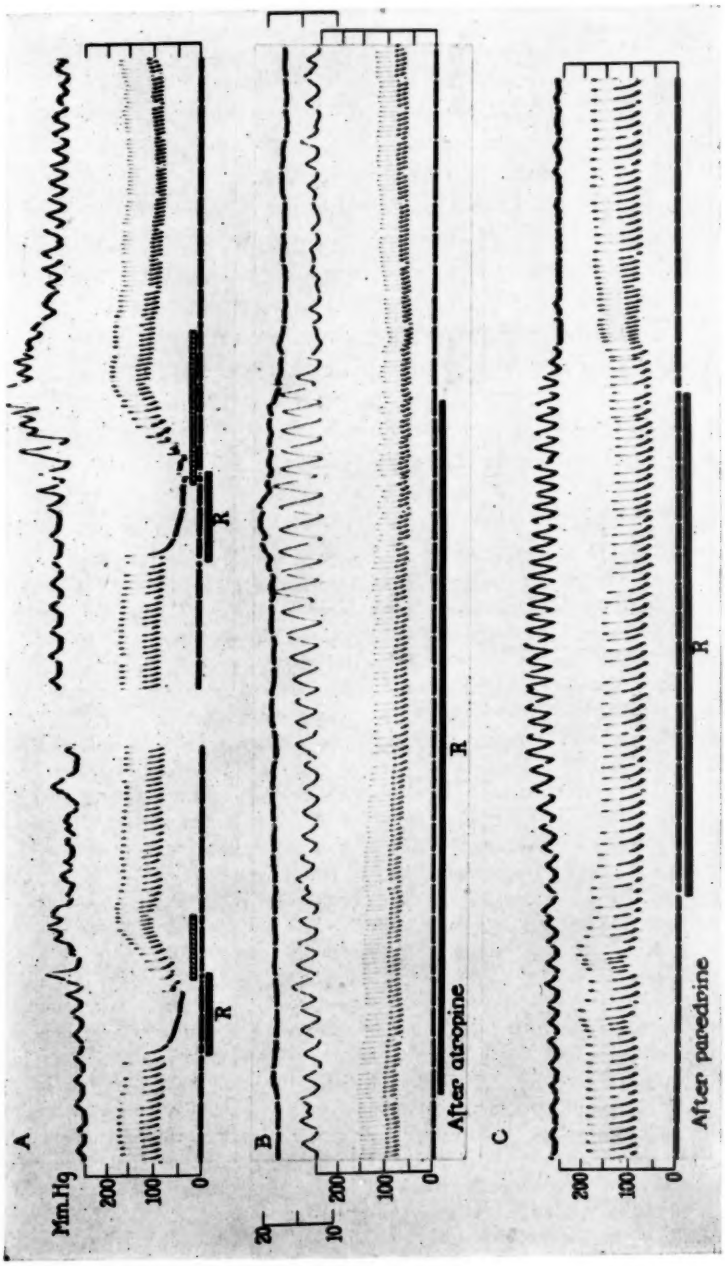

Fig. 1.—In this figure and in the subsequent ones, the upper curve represents respiration (inspiration is the upstroke), as recorded by a pneumograph, and the lower curve, arterial pressure, as recorded by a Hamilton manometer from the radial artery. The base line is interrupted at intervals of five seconds. The solid line below the base line indicates the duration of stimulation of the carotid sinus (R—right side, L—left); the hatched line above shows the duration of syncope and convulsions.

An example of the vagal response to carotid sinus pressure is shown (*A*). Slowing of the pulse and convulsions were prevented by atropine (*B*), but the depressor response was marked. Paredrine also prevented convulsions, but moderate slowing and some fall in arterial pressure persisted (*C*). Note hyperpnea, followed by shallow, irregular respirations (*B*) and apnea (*C*). The curve above respiration (*B*) is a record of venous pressure.

paredrine hydrobromide. Paredrine was employed in preference to other sympathomimetic substances because its effect is supposed to be unaccompanied by cortical stimulation.[22, 23]

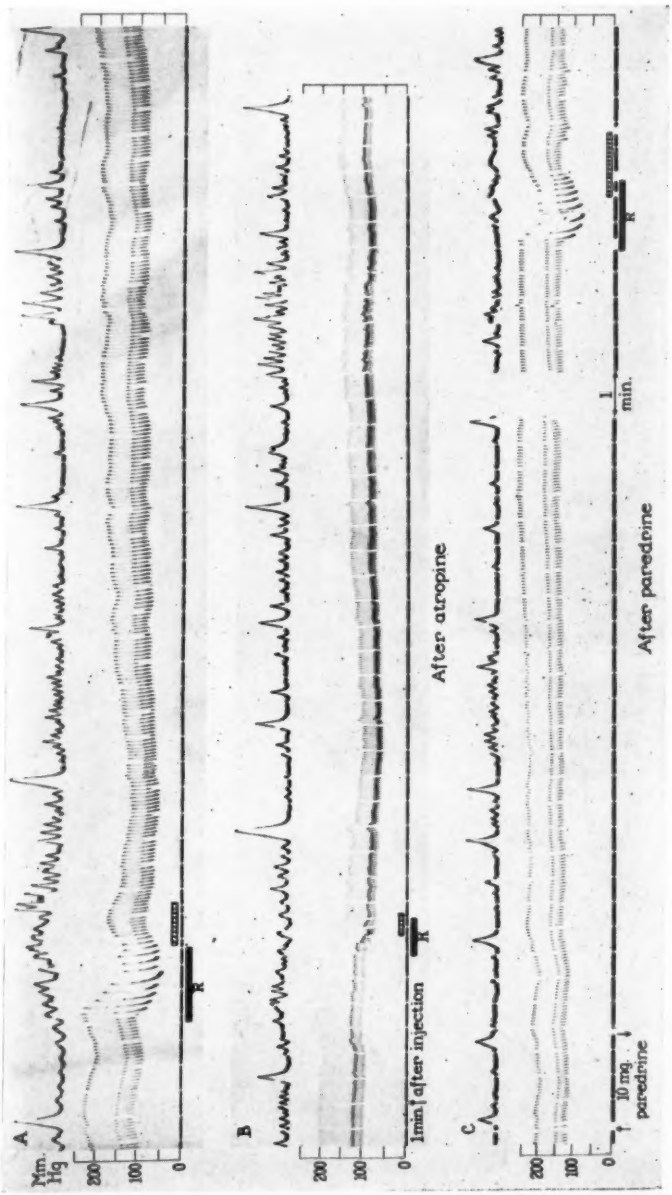

Fig. 2.—An example of the coexistence of vagal and depressor responses with syncope and convulsions is shown (*A*). Atropine prevented the vagal, but enhanced the depressor, response (*B*). Syncope and convulsions persisted. Paredrine caused a moderate rise in arterial pressure and prevented the depressor, but not the vagal, response and syncope (*C*).

Bradycardia, and often asystole of three to seven seconds' duration, and a fall in arterial pressure constituted the evidence for circulatory effects of carotid sinus stimulation. If both pulse rate and arterial pressure returned promptly to their previous levels, the fall in arterial

pressure was taken to be the result of slowing of the heart, and the response was called "vagal" (Cases 1, 2, 3, Fig. 1*A*). Additional evidence that a fall in arterial pressure was, in these instances, mainly dependent upon the bradycardia was the fact that, when atropine prevented the slowing of the heart, it also prevented, to a large extent, the fall in arterial pressure (Fig. 1*B*).

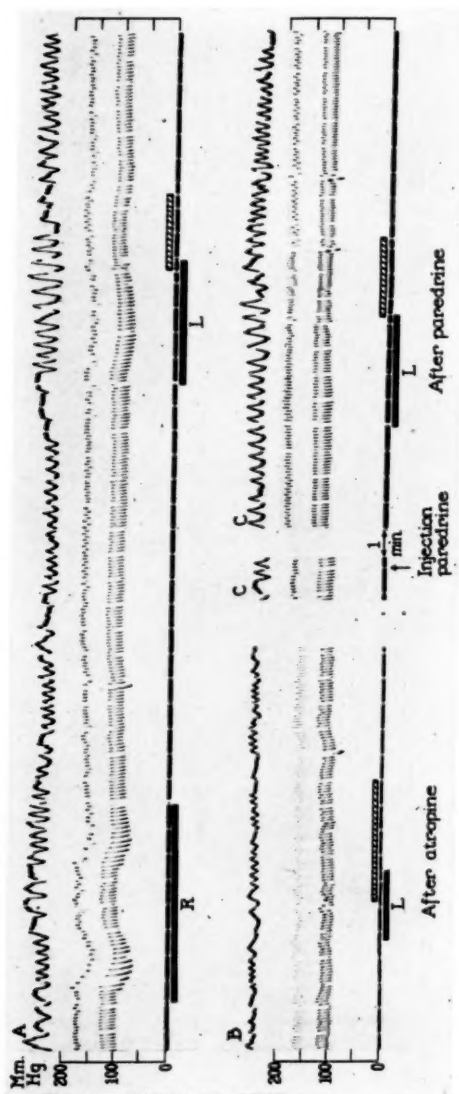

Fig. 3.—"Cerebral type" of response to stimulation of the carotid sinus is shown. Syncope and convulsions failed to occur in the presence of moderate circulatory changes on stimulation of the right side, but occurred promptly in the absence of circulatory changes on stimulation of the left (*A*). Atropine (*B*) and paredrine (*C*) failed to prevent syncope and convulsions.

In a considerable number of instances the fall in arterial pressure outlasted the slowing of the heart (Cases 4 to 15, Fig. 2*A*). A "depressor," as well as a "vagal," response was obviously present, for the intravenous injection of atropine prevented the slowing of the heart

rate but not the fall in arterial pressure. Under the influence of this drug, the fall in pressure was often greater than before its injection (Fig. 2*B*). In two instances (Cases 4 and 6), the arterial pressure remained low for several hours. The injection of paredrine had the opposite effect—the "depressor" reaction was abolished, but the "vagal" effect persisted even though it was usually less intense (Fig. 2*C*). A purely depressor response was not observed in the present study except after the administration of atropine. Its occurrence has, however, been reported.[8, 10, 18, 24] It should be noted that the right and left carotid sinuses of a given person often exhibit very different degrees of sensitivity, and may even give rise to qualitatively different responses (Figs. 3 and 4, Table I).

Relation of Circulatory Changes to Syncope.—In the presence of marked circulatory disturbances caused by carotid sinus stimulation, it seemed likely that the occurrence of syncope was attributable to cerebral anoxemia due to asystole and a fall in arterial pressure. This belief was strengthened by the fact that when circulatory changes failed to occur or were very slight after the administration of atropine or paredrine, syncope, too, failed to develop (Fig. 1).

There were, however, five subjects (Cases 13, 14, 15, 16, and 17) who had syncope without circulatory disturbances. Three of these had marked circulatory changes, to which syncope was attributed before atropine or paredrine was given, but, when syncope persisted in spite of the prevention of marked circulatory disturbances by means of these drugs, it became clear that the two were not related. Weiss and Baker[17] have described similar instances.

In two instances (Cases 16, 17), syncope with or without convulsions was frequently observed to follow digital pressure on the carotid sinus in the *absence* of significant systemic circulatory change (Figs. 3*A*, 4*B*). Syncope occasionally occurred after five, but usually after ten or fifteen, seconds of pressure. The administration of atropine and paredrine did not prevent the occurrence of syncope (Figs. 3*B* and *C*). These observations demonstrate that there is a "cerebral" type of carotid sinus syncope, for the syncope was shown not to be related to circulatory disturbances.

The type and degree of circulatory changes elicited in these patients by stimulation of the right and left carotid sinuses differed markedly. That syncope and convulsions may occur on stimulation of the side which produces the lesser degree of circulatory change and may fail to occur on stimulation of the side which causes the more marked circulatory response (Figs. 3 and 4, Table I) makes it obvious that the occurrence of syncope and convulsions with carotid sinus stimulation is not always related to an impaired flow of blood to the brain.

Venous Pressure.—Observations upon animals' mesenteric veins which were isolated from the circulation but left in connection with their

nervous attachments have shown that contraction takes place during stimulation of the carotid sinus.[25, 26, 27] Studies of the effect of stimula-

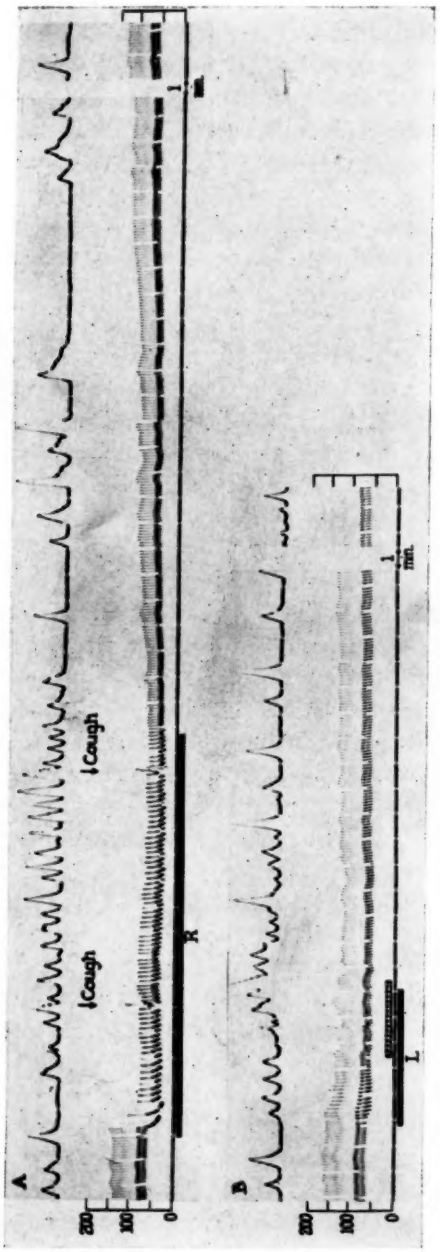

Fig. 4.—A second example of "cerebral" response is shown. Marked vagal and depressor responses followed stimulation on *right* side, without syncope or convulsions (*A*). Stimulation on the *left* was followed by syncope and convulsions *in the absence* of significant circulatory changes (*B*).

tion of the carotid sinus in man upon venous pressure are too few to draw conclusions. A rise during convulsions only,[28] a fall with slowing of the heart,[29] and failure to change during the cerebral type of carotid sinus

syncope[18] have been reported. The changes were independent of arterial pressure.

In seven patients with a vagal and depressor type of circulatory response, the venous pressure rose promptly, but slightly (1 to 2 cm. of water), as the heart rate slowed and the arterial pressure fell, and returned quickly to the previous level along with the heart rate and arterial pressure. A rise in venous pressure always preceded syncope and convulsions, even in one instance of a purely cerebral type. During pressure on the common carotid artery *below* the carotid sinus, a slight fall occurred, together with a rise in arterial pressure and heart rate. In each case the change in pressure was in a direction that might accompany the probable changes in cardiac output.

RESPIRATORY RESPONSES

In man, hyperpnea occurs quite regularly on pressure in the region of the carotid sinus, independently of circulatory changes, and may be elicited in nearly all normal persons,[36, 37, 38] as well as in those who have an abnormal circulatory response to carotid sinus pressure.[18, 39] Some observers[18, 28] have stated, however, that the incidence of hyperpnea is greater in elderly and arteriosclerotic persons. In order to clarify this point, two groups of persons were studied, one elderly, the other young.

The respiratory changes caused by digital pressure in the region of the carotid sinus in fourteen elderly patients in the present study who also exhibited marked circulatory responses were not different from those which occurred in persons who did not exhibit circulatory changes or those reported previously in man. A marked increase in the depth, with little or no increase in the rate, of respiration occurred. Apnea, as the initial response, was not observed, regardless of the type of circulatory response. Hyperpnea occurred with the cerebral (Fig. 3), as well as with other types of syncope and, in the absence of syncope, both before and after the administration of atropine and paredrine (Fig. 1). It seemed to be independent, likewise, of circulatory change.

In those instances in which syncope and convulsions were prevented by the administration of atropine or paredrine, it was possible to observe respiratory changes during prolonged stimulation of the carotid sinus. The respiratory excursions began to increase in depth within 5 to 20 seconds after pressure was applied and continued to do so until a peak was reached between 45 and 90 seconds, and then declined rapidly during the next 10 or 15 seconds. The rate of respiration usually increased two to five breaths per minute (Fig. 1). Often it remained unchanged, and, in one instance, decreased. Although pressure on the sinus was continuous, a phasic type of respiration often occurred which resembled, in some instances, Cheyne-Stokes respiration (Figs. 5*A*, *B*, *C*). Each succeeding hyperpneic period was, however, usually shorter and less intense than the previous one. In the intervening periods the

respiratory excursions were either shallow and irregular, with periods of apnea, or were simply shallow and slower than normal. During hyperpnea, dizziness, "lightheadedness," a burning sensation in the face, tingling in the extremities, and, in many instances, profuse perspiration of the hands and flushing of the face occurred. The degree of hyperpnea appeared to be sufficient to account for these symptoms.

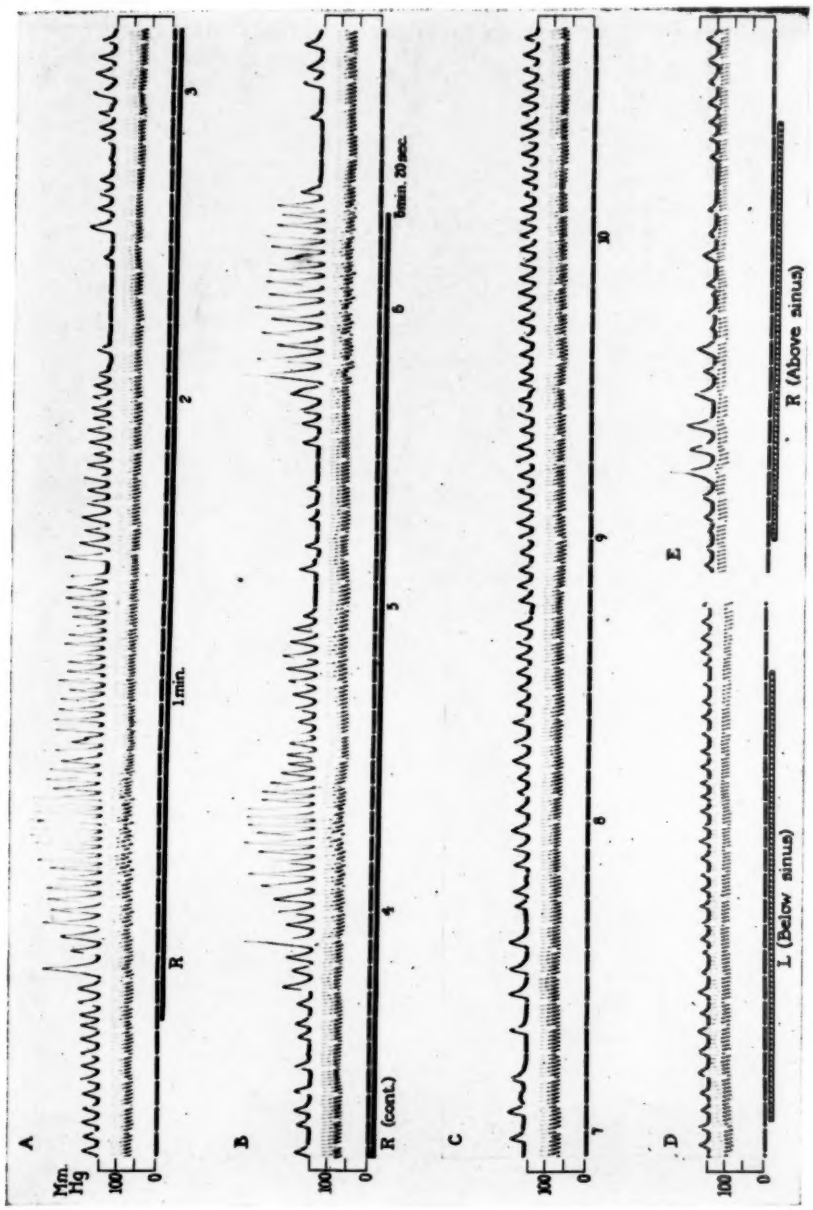

Fig. 5.—Periods of hyperpnea followed by periods of apnea and irregular breathing induced by continuous prolonged pressure upon the carotid sinus of a young adult are shown (*A*, *B*, and *C* are three immediately successive portions of a continuous record). Circulatory changes occurred only at the height of hyperpnea. Respiration was not altered by digital pressure *below* the carotid sinus (*D*) and only slightly during the first few seconds of pressure *above* (*E*).

Changes in the character of respiration were not observed when pressure was applied to the common carotid artery above or below the level of the carotid sinus (Fig. 5*D, E*), except for occasional deep breaths just after pressure was begun (Fig. 5*E*). Pain as a result of digital pressure was clearly not responsible for the stimulation of respiration, for painful stimuli (strong pressure on the trachea or the anterior border or belly of the sternocleidomastoid muscle, or deep pressure elsewhere in the neck) did not elicit a similar response. Furthermore, when the skin in the region of the carotid sinus was anesthetized with a 1.5 per cent solution of procaine, respiratory stimulation could still be elicited by pressure over the carotid sinus.

Thirty-five young persons were also studied. None of them exhibited pronounced circulatory responses to carotid sinus pressure. Twenty-two (thirteen men and nine women) were patients from the wards, and thirteen (eight men and five women) were members of the house and nursing staffs. Their ages ranged from 15 to 30 years. In all but five persons, the hyperpnea in response to carotid sinus pressure was similar in degree to that which occurred in the older patients. The respiratory change was usually not preceded by significant circulatory changes, but occasionally there were a slight rise in arterial pressure (5 to 20 mm. Hg) and a slight fall in pulse rate (6 to 20 per minute). When phasic respiration was induced by prolonged pressure on the sinus, changes in the character and rate of the pulse occurred only during the height of the hyperpneic periods, and subsided during the apneic periods (Figs. 5*A* and *B*). This phenomenon also occurs with true Cheyne-Stokes respiration.[40] Observation of these two groups tends to confirm the view expressed by Danielopolu and his co-workers, namely, that hyperpnea in response to carotid sinus pressure occurs in most normal persons, young or old, male or female.

Mechanism of Production of Hyperpnea.—There is, in the literature, general agreement that changes in the arterial pressure within the carotid sinus influence respiration as well as circulation. The circulatory changes described in man in response to pressure on the carotid sinus have quite regularly resembled those observed in animals, but respiratory reactions in man are not so easily correlated with the studies on animals. In animals under anesthesia, an increase in arterial pressure within the carotid sinus gives rise to apnea or slowing of respiration,[12, 13, 30-35] but hyperpnea is the regular response to pressure in the region of the carotid sinus in man.

The conditions under which studies of respiratory response to stimulation of the carotid sinus and carotid bodies in animals have been carried out differ, however, from those under which man has been studied chiefly in three respects: (1) the animals were anesthetized, (2) the pressure changes were applied within the carotid sinus, rather than upon it from the outside, and (3) anatomic and physiologic

arrangements were carefully made so that stimulation of the carotid sinus would not affect the carotid body. Any of these differences may account for the fact that apnea, rather than hyperpnea, usually occurs in animals when there is an increase in pressure in the carotid sinus.

An attempt was made to investigate the first of these differences by testing the respiratory effects of pressure on the sinus while the subject was under the effect of general anesthetic agents, and to study the third by using local anesthesia to separate the activities of the carotid sinus from the carotid body. Concerning the anesthetic agents employed in animal studies, it is generally agreed that the barbiturates depress the carotid sinus, vasomotor[14, 41] and respiratory reflexes,[42] and that chloralasane is the one of choice,[42, 43] but lack of agreement exists concerning the use of morphine-pernocton anesthesia.[43, 44] In human beings, barbiturates and many of the inhalation anesthetic agents are reported to depress, and morphine to increase, the circulatory reflex.[45]

The effect of barbiturate anesthesia was studied on six patients who showed respiratory, but no circulatory changes in response to carotid sinus pressure. Anesthesia of sufficient degree to prevent any response to painful stimuli was induced by injecting, intravenously, evipal (4 cases) or sodium pentothal (2 cases) (0.6 to 1.0 Gm.). A transient, slight fall of arterial pressure, without significant change in pulse rate, usually followed the injection. Hyperpnea of the same degree and after the same interval as in the unanesthetized state was elicited in every case. In the doses used, barbiturate anesthesia plainly did not affect the respiratory reaction. In one instance a preanesthetic dose of ¼ grain of morphine and $\frac{1}{100}$ grain of scopolamine was followed by drowsiness, but failed to prevent the appearance of hyperpnea after pressure on the carotid sinus. It seems unlikely, therefore, that general anesthesia is responsible for the differences observed between man and animals.

In studies on animals, great care has been taken not to alter the blood supply to the carotid body during stimulation of the carotid sinus. The method generally employed has been to exclude the carotid body from the circulation, and to perfuse it independently. Under these circumstances, respiration is depressed when there is an increase in intrasinal pressure. When the blood supply to the carotid body is, however, deliberately reduced, respiration is stimulated.[46, 47] In man the two structures lie so close together that during pressure upon the carotid sinus region the blood supply to the carotid body may obviously be partially obstructed. It is, therefore, quite possible that the hyperpnea observed in man may arise as a result of stimulation of the carotid *body* rather than of the carotid *sinus*.

To test this possibility, the regions about the carotid sinuses of four persons were anesthetized with a 1.5 per cent solution of procaine to learn whether the respiratory response, like the circulatory response to

pressure upon the carotid sinus, could be prevented. Three exhibited marked circulatory and respiratory changes, and one had respiratory changes only. The degree of success of the block was tested by injecting 0.11 mg. per kilogram of body weight of sodium cyanide intravenously. If hyperventilation occurred after the injection of sodium cyanide, more procaine was injected, but if there was no response, the block was considered complete. It was found that when sodium cyanide failed to elicit a respiratory reaction, pressure on the carotid sinus also failed. Circulatory responses likewise were lacking. As the anesthesia wore off, the respiratory response (hyperpnea) returned more quickly than the circulatory (cardiac slowing)—a fact which suggests that the mechanisms involved in bringing about the two responses are not identical. Together with the previous studies on animals, the observation suggests that hyperpnea, as ordinarily induced by digital pressure in man, is caused by a disturbance of the circulation to the carotid body.

Marked transient tachycardia and hypertension, lasting thirty or forty minutes, which were not affected by carotid sinus pressure, occurred after complete anesthetization of both carotid sinuses; this was to be expected, in view of Heyman's studies on dogs whose carotid sinus and aortic nerves had been sectioned.[12]

COMMENT

In persons with a hypersensitive carotid sinus reflex, syncope and convulsions seem to be brought about in at least two ways. The one which is better understood and more common is probably the result of cerebral anoxemia caused by slowing of the heart, or asystole, or a fall in arterial pressure. The second mechanism occurs in the absence of systemic circulatory changes of any significance, for which reason it has been labelled the "cerebral" type. Gross cerebral circulatory changes, as measured by a thermocouple and by differences in oxygen and carbon dioxide content of arterial and venous blood, apparently do not occur in this variety.[18, 48] Vasoconstriction in small areas of the brain of insufficient extent to be detected by these techniques may, of course, have taken place, but it seems unlikely; for, in animals, dilatation of the cerebral vessels has been demonstrated on stimulation of the carotid sinus (increase in intrasinal pressure), and constriction only on decrease of intrasinal pressure.[49, 50] In any event, the vasomotor reactions of the blood vessels of the brain are feeble, and do not ordinarily appear to play a large part in the control of cerebral blood flow.[50, 51, 52]

Some evidence exists for believing that syncope occurs as the result of direct nervous transmission of impulses from the site of stimulation. Weiss believed that syncope may result from reflex inhibition of a center of consciousness.[53] Electroencephalographic studies indicate that some alteration in cerebral activity occurs during the "cerebral" type of carotid sinus syncope, but a distinction cannot be drawn between this type of syncope and that associated with systemic circulatory change.[54]

The regular occurrence of hyperpnea in man is of interest because it differs from what has been reported in studies on animals. With the exception of Danielopolu and his co-workers,[37, 38, 39] it is generally agreed that apnea is the usual response to a rise in *intrasinal* pressure. Schmidt and Comroe[34] have found that if the effect of compensatory reflex areas (opposite carotid sinus and aortic bodies) is not eliminated, either by denervation or by maintaining the systemic blood pressure at a constant level, hyperpnea may occur. In the present study it seems unlikely that compensation accounts for the hyperpnea for two reasons. First, hyperpnea occurred in the absence of circulatory changes of sufficient magnitude to arouse a compensatory reaction, and, second, it occurred to the same degree and quite as promptly in two patients whose left carotid sinuses had been removed surgically[55] (Cases 12 and 14). The aortic bodies were, of course, intact in both patients.

The more likely explanation is that the crude manner in which stimulation of the carotid sinus is carried out in man, namely, by pressure on the neck in the region overlying the carotid sinus, impairs the blood flow through the carotid body. Four facts suggest that this is so. (1) The carotid body and sinus lie in close proximity in man. (2) Pressure is required for a considerably longer period of time to bring on hyperpnea than to induce cardiac slowing. (3) After local anesthetization of the region of the carotid sinus, the respiratory and circulatory responses returned independently of each other; the circulatory took longer. (4) The respiratory response (hyperpnea) corresponds to what has been found in animals when the blood flow to the carotid body is reduced. Differences between animal and human studies become, from this point of view, more understandable.

Even though the method of stimulation in man is obviously crude insofar as localization is concerned, it is surprising that standard textbooks of physiology fail to refer to the observation that hyperpnea regularly follows pressure on the neck in the region of the carotid sinus in normal persons, as well as in those with evidence of a hypersensitive carotid sinus reflex, and that it is quite independent of circulatory change.

SUMMARY AND CONCLUSIONS

1. The circulatory and respiratory responses to stimulation of the carotid sinus by digital pressure in seventeen persons with hypersensitivity of the carotid sinus were studied.

2. The common circulatory response is slowing of the heart and asystole (vagal response), together with a fall in arterial pressure (depressor response). A pure vagal response is next most common. A pure depressor response was not observed except when the patient was under the influence of atropine. Paredrine hydrobromide prevented, to a large degree, the depressor responses.

3. Two patients had convulsions without any significant circulatory change (cerebral type). In three other patients, syncope and convulsions persisted when circulatory changes were inhibited by the administration of atropine or paredrine.

4. Hyperpnea is the regular respiratory response to digital pressure in the region of the carotid sinus. Its occurrence is independent of the circulatory response. It is independent of age or sex. It is not prevented by barbiturate anesthesia, but local infiltration of the region about the carotid sinus and carotid body with procaine hydrochloride abolishes it. Prolonged stimulation is often followed by a phasic type of respiration similar to Cheyne-Stokes breathing.

5. Evidence is presented for the belief that hyperpnea after pressure on the neck in the region of the carotid sinus in man may be caused by a disturbance of the blood supply to the carotid body, rather than by mechanical stimulation of the carotid sinus.

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EFFECT OF HIGH-PROTEIN DIET AND UREA ADMINISTRATION ON THE BLOOD PRESSURE OF NORMAL DOGS AND OF DOGS WITH EXPERIMENTAL RENAL HYPERTENSION

JOHN L. GUERRANT,* M.D., JAMES K. SCOTT, M.D., AND
J. EDWIN WOOD, JR., M.D.
CHARLOTTESVILLE, VA.

A NUMBER of observations have been made to ascertain the effect of high-protein diet on renal function and structure. Newburgh[1] and others produced renal lesions in animals by high-protein feeding. Relatively few investigators have studied the question of blood pressure response to high-protein diet. Almost all agree that excessive protein intake does not cause blood pressure elevation in normal, intact animals. An exception appears in the work of Nuzum, Osborne, and Sansum,[2] who attributed a blood pressure rise in rabbits to renal injury produced by excessive urinary acidity from a high-protein, acid ash diet (oat protein), or excessive urinary alkalinity from a high-protein, alkaline ash diet (soy bean). Anderson,[3] however, failed to find any blood pressure increase in normal rabbits which were maintained on a high-protein diet for nearly a year, or in rabbits in which 60 per cent of the kidney tissue had been removed. Chanutin and Ludwig[4] rendered rats hypertensive by subtotal nephrectomy, and, in subsequent feeding experiments, considered the type of protein component an important factor in the incidence of hypertension in these animals.

These experiments on rabbits and rats present three general disadvantages: first, the relative uncertainty of sustained hypertension after partial renal ablation; second, lack of suitable methods for repeated systolic and diastolic blood pressure observations; and, third, the fact that rabbits and rats are unaccustomed to high-protein diets.

More recently, Verney and Vogt[5] reported rises of blood pressure after feeding meat, urea, and salt to dogs which had been rendered hypertensive by the application of silver clamps to the renal arteries. Maclachlan and Taylor[6] studied a single dog which was made hypertensive by the application of a cast to one kidney and removal of the other. Repeated rises of mean blood pressure followed meat and urea feeding. Philipsborn, Katz, and Rodbard[7] found that high-protein diets had no effect on the blood pressure of normal dogs, but a single animal out of four with severe hypertension showed a sharp rise of systolic and diastolic blood pressure on a meat diet. Smaller elevations

From the Department of Internal Medicine and the Department of Pathology, University of Virginia Medical School, Charlottesville, Va.
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*DuPont Fellow in Medicine.

of blood pressure occurred in two repetitions of this original observation. A high-protein diet had no effect on the blood pressure of the other three hypertensive dogs, or on three additional dogs with mild hypertension.

It is the purpose of this paper to describe the blood pressure reactions of normal and hypertensive dogs to the administration of large amounts of meat and urea.

METHODS

The dogs were large mongrels or hounds. An effort was made to select dogs with long, slender legs. Only quiet animals were used. Each dog was kept in an individual cage and fed on a standard kennel ration.*

Hypertension was produced by the method of Goldblatt, et al.[8] One of the renal arteries was exposed by means of a flank incision, a clamp was placed on it and tightened until no pulsations distal to it could be felt, and then the screw was released three-quarters to one and one-half turns. About two weeks later a similar procedure was done on the other side. Five months to six years elapsed between the completion of the last stage of the operation and the beginning of the experiments described in this report.

Blood pressures were taken by direct puncture of the femoral artery, and recorded with the Hamilton manometer.[9] The animals were trained to lie quietly, and the needle was inserted into the femoral artery without anesthesia. As a rule, this procedure disturbed the animals very little, for all of them had been trained for at least five months before the beginning of the experiments.

Blood urea estimations were made in duplicate by the method of Van Slyke and Cullen.[10] None of the animals had enough renal insufficiency to cause an abnormally high blood urea.

EFFECT OF FEEDING A HIGH PROTEIN DIET OVER A PROLONGED PERIOD

Four hypertensive and two normal dogs were selected. One of the hypertensive dogs was accidentally killed and another became pregnant, so that only two hypertensive and two normal dogs were left to complete this study. Blood pressures were taken once or twice a week throughout the experiment. For two weeks the dogs were kept on the regular kennel ration, and then the diet was changed to 36 Gm. of lean raw beef per kilogram of body weight for five weeks. The amount was then increased to 73 Gm. per kilogram for four weeks, and, finally, during the last two weeks, they received 110 Gm. of meat per kilogram. This amounted to more than 4 pounds of meat a day for the larger dogs. A second control period of eight weeks on the kennel ration finished the experiment. All of the dogs gained weight during the second and third meat-feeding periods. A maximum urea level of 100 mg. per 100 c.c. of blood was observed in one of the hypertensive dogs while it was on the meat diet. Fig. 1 shows all of the blood pressures and weights during this experiment. One of the hypertensive dogs (No. 42) seemed to show a constant rise in blood pressure while on the meat diet, but his pressure did not fall when he was changed back to the kennel ration. In the other animals no definite changes were noted.

*Cracklins, shredded wheat, oatmeal, buttermilk, bran, alfalfa salt, cod-liver oil, and meat scraps. Approximate composition: protein, 52 per cent, fat, 6 per cent carbohydrate, 36 per cent, fiber, 4 per cent.

EFFECT OF A SINGLE, LARGE, HIGH-PROTEIN MEAL

Six dogs were used for this experiment. Four had bilateral Goldblatt clamps, with resultant hypertension, and two were normal animals. After a twenty-four-hour fast, the dogs were given three pounds of lean raw beef at a single meal. Two of them (Nos. 42 and 49) ate only about half of the meat. The others took the entire ration. The blood pressure was recorded just before the meal and at one hour, two hours, four hours, and twenty-four hours after. In most instances the blood pressure was taken on the day preceding the experiment, as well. The

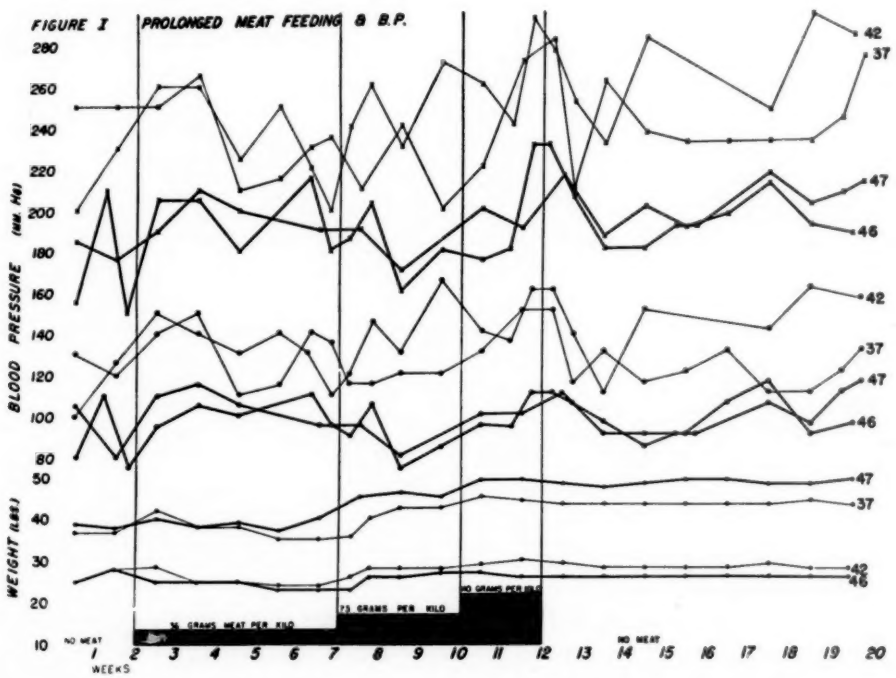

Fig. 1.—Graphic record of blood pressure and weight of two hypertensive dogs (light lines) and two normal dogs (heavy lines) fed on regular kennel ration, lean raw meat, and kennel ration again.

blood pressures appear in Table I. It will be noted that the changes are relatively slight and inconstant. In two of the hypertensive dogs there was a slight immediate rise in pressure, in one there was a slight fall, and in the fourth there was no significant change. The blood pressure of the control animals remained essentially unchanged after meat feeding.

EFFECT OF INTRAVENOUS ADMINISTRATION OF UREA ON BLOOD PRESSURE

Two normal and four hypertensive dogs were used in this experiment. After ascertaining the blood pressure and blood urea levels, 1½ Gm. of urea per kilogram of body weight were given intravenously as a 50 per

TABLE I

BLOOD PRESSURES BEFORE AND AFTER A LARGE MEAL OF LEAN RAW MEAT
(Dogs 37, 40, 42, and 44 Had Goldblatt Clamps on Both Renal Arteries; Dogs 49 and 53 Were Normal)

DOG NO.	PRECEDING DAY	BEFORE MEAL	ONE HOUR AFTER MEAL	TWO HOURS AFTER MEAL	FOUR HOURS AFTER MEAL	TWENTY-FOUR HOURS AFTER MEAL
37	225/130	240/130	220/130	240/130	230/125	260/155
40		200/115	230/120	200/115	220/120	220/120
42	265/150	280/160	300/170	280/155	240/155	280/170
44		245/130	230/130	270/140	245/130	245/130
49	190/100	210/100		200/105	180/ 90	200/100
53	180/100	200/100	180/ 90		205/ 95	215/115

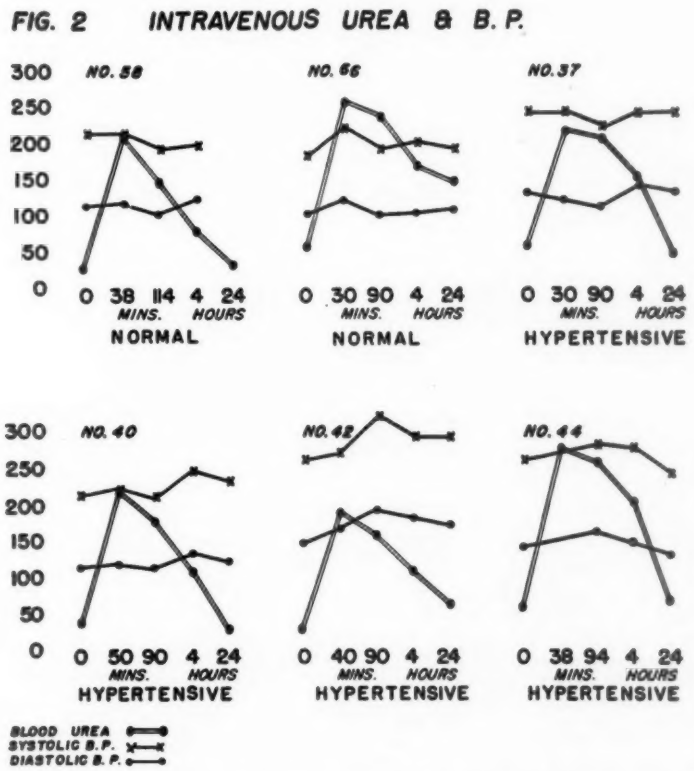

Fig. 2.—Graphic record of blood pressure and blood urea after intravenous administration of urea to normal and hypertensive dogs.

cent solution. The urea was given by means of a small rubber tube which was inserted intravenously before the beginning of the experiment, so that no discomfort to the animal accompanied the injection. The blood pressure and blood urea were ascertained at about one-half hour, one and one-half hours, four hours, and twenty-four hours after the urea injection. There was always a marked rise in blood urea, but the level promptly returned to normal within twenty-four hours. The

blood pressure and blood urea changes are shown in Fig. 2. One of the normal dogs showed a slight rise in blood pressure, and the other showed no definite change. One of the hypertensive dogs (No. 42) showed a definite rise in blood pressure, another (No. 44) showed a slight rise, and two showed no change.

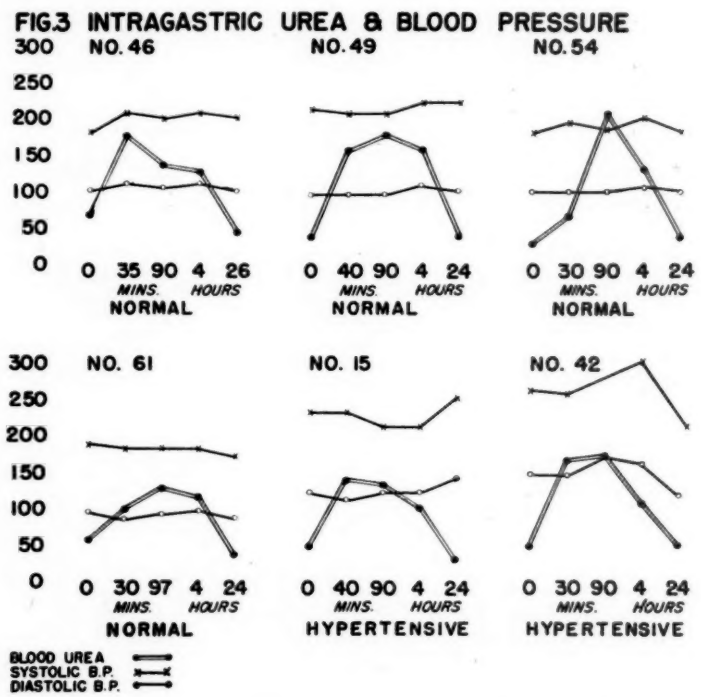

Fig. 3.—Graphic record of blood pressure and blood urea after administration of urea by stomach tube to normal and hypertensive dogs.

EFFECT ON BLOOD PRESSURE OF UREA ADMINISTERED BY STOMACH TUBE

Two hypertensive and four normal dogs were used for this experiment. The basal blood pressure and blood urea levels were ascertained, and each dog was given 1½ Gm. of urea per kilogram of body weight by means of a stomach tube. Subsequently, blood pressure and blood urea observations were made at approximately one-half hour, one and one-half hours, four hours, and twenty-four hours. In each case there was a prompt and marked rise in blood urea, but the level returned to normal within twenty-four hours. The blood pressure and blood urea changes are shown in Fig. 3. In only one of the dogs (No. 42), a hypertensive animal, was there a definite change in blood pressure. In this dog the systolic pressure rose approximately 50 mm. Hg and the diastolic pressure approximately 25 mm. Hg one and one-half hours after urea administration.

DISCUSSION

In these experiments, prolonged meat feeding, the feeding of a single, large, meat meal, and the administration of urea by vein or by stomach tube failed to produce consistently significant blood pressure changes in normal and hypertensive dogs. One of the hypertensive dogs (No. 42) showed a moderate elevation of blood pressure during each of the experiments. However, the blood pressure failed to return toward the normal level during the eight-week control period after the prolonged meat diet. In the other hypertensive and normal dogs the changes were either insignificant or inconstant. These results are similar and comparable to those of Philipsborn, Katz, and Rodbard,[7] who observed a significant elevation of blood pressure in only one of their hypertensive dogs. Our results differ somewhat from those of Verney and Vogt,[5] who fed hypertensive dogs meat, salt, and urea, and produced slight changes in the systolic blood pressure. Their dogs were rendered hypertensive by the method of Goldblatt, et al.,[8] and the blood pressures were taken by the Van Leersum loop method.[11] In two dogs with bilateral renal ischemia the blood pressure rise was 24 mm. Hg and, in two of three dogs with a single ischemic kidney, 16 and 20 mm. Hg, respectively. The third dog of this last group failed to show any blood pressure change. In our experience, systolic blood pressure changes of this order occur spontaneously in both normal and hypertensive dogs.

The observation of Maclachlan and Taylor[6] on a single dog which had been rendered hypertensive by a cast on one remaining kidney requires brief comment. These investigators failed to state what blood pressure method was used, but, assuming that they measured the mean arterial pressure by arterial puncture, the rise may be considered significant, particularly when the same order of response occurred twice, with a return to original levels each time. It would be interesting to know whether or not this experiment could be repeated on other dogs. The occasional hypertensive response to meat feeding in dogs which have been rendered hypertensive by the Goldblatt method may be caused by poor development of the capsular circulation after operation, and, conversely, failure of response in the Goldblatt type of animal may be associated with an excellent capsular collateral circulation. Other indirect evidence suggests the same thing. A previous study by Jolliffe and Smith,[12] later confirmed by Van Slyke, Rhoads, Hiller, and Alving,[13] showed that dogs have a higher urea clearance on a high-protein diet than on a low-protein diet. The latter group of investigators added the observation that the urea clearance was found to vary in direct proportion to renal blood flow. It seems not unlikely that some dogs with renal artery clamps will develop a less adequate capsular collateral circulation than others, and hence relatively inadequate renal blood flow after a large protein meal. In such a case, added degrees of hypertension may follow meat feedings. This suggests the advisability of further meat-feeding experiments on dogs which have been rendered hyperten-

sive by placing a cast on one kidney and removing the other. In such an experiment, perirenal collateral circulation would not occur.

It seems clear from the literature and our own observations that meat feeding will not bring about a blood pressure rise in normal dogs. The status of this question in respect to dogs with experimental hypertension produced by reduced renal blood flow is not clear, but it may possibly be related to the degree of re-established capsular circulation.

SUMMARY

The administration of a high-protein diet (lean raw meat) to normal and hypertensive dogs for a long or short period of time failed to produce a consistent rise or fall in systolic or diastolic blood pressure.

The administration of urea, intravenously or by stomach tube, to normal and hypertensive dogs likewise failed to produce any significant change in blood pressure.

In one hypertensive dog there was a slight to moderate rise of systolic and diastolic blood pressure after each of the four experimental procedures.

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CARDIAC COMPLICATIONS IN ACUTE GLOMERULONEPHRITIS

HOWARD M. ODEL,* M.D., AND WILLIAM S. TINNEY,† M.D.
ROCHESTER, MINN.

INVOLVEMENT of the heart in acute glomerulonephritis has been recognized for many years, but until recently very little attention has been given to it. In 1879, Goodhart[1] reported five cases of "scarlatinal dropsy." Necropsy was done in four of these cases and dilatation of the right and life sides of the heart was found. In one case severe anasarca was present. Goodhart was unable to find any evidence of valvular heart disease in these cases and concluded that the cardiac failure was caused by "sudden peripheral obstruction in the circulation and degenerative changes in the cardiac muscle."

In 1881, Silbermann[2] reported five cases of acute nephritis in which there were hypertrophy and dilatation of the left ventricle. In one of these cases there was pulmonary edema. Steffen,[3] in 1882, reported a case of acute nephritis in which severe dyspnea and cyanosis were observed. In 1889, Hutinel[4] stressed the importance of considering the possibility of acute nephritis in every case of acute cardiac dilatation in which there is no other demonstrable evidence of cardiac disease. Nobécourt and Voisin,[5] working in Hutinel's Clinic in 1909, collected data on twelve cases of acute nephritis in which dilatation of the heart was noted. They agreed with Hutinel that when no valvular lesion can be found, cardiac failure should be considered pathognomonic of acute nephritis. Nobécourt and Voisin expressed the belief that the hypertrophy and dilatation of the left ventricle in these cases could not be ascribed to hypertension alone, but that the generalized infection was an important factor.

In 1917, Franke[6] reported sixty-seven cases of acute nephritis in which roentgenographic examination of the heart had been made. In 75 per cent of these cases there was cardiac enlargement which was believed to be a combination of hypertrophy and dilatation. Volhard[7] observed evidence of myocardial insufficiency in the first few days of acute nephritis. Clinically, he reported strong heart action, accentuation of the second sound at the base, presystolic gallop rhythm, and, fairly frequently, a systolic murmur at the apex caused by relative myocardial insufficiency and stretching of the mitral ring. The apical impulse was heaving, and the area of cardiac dullness was increased. Volhard men-

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*Division of Medicine, Mayo Clinic.
†Fellow in Medicine, Mayo Foundation.

tioned the grave prognostic significance of a sudden fall of blood pressure or a considerable acceleration of the pulse rate in acute nephritis. At necropsy he observed dilatation of the left ventricle in these cases.

In 1920, Alwens and Moog[8] studied four cases of acute nephritis by means of serial orthodiagrams, and demonstrated cardiac enlargement during the acute infection, with return to normal size when the patients recovered. They expressed the belief that the enlargement was caused by acute dilatation and by hydropericardium.

Christian and O'Hare,[9] in 1925, concluded that any cardiac enlargement, murmurs, or arrhythmia observed in a patient who had acute nephritis was coincidental, and in no way related to the nephritis. They maintained that, except in rare cases, the heart and circulation are unchanged in acute nephritis.

In 1930, Levy[10] reported ten cases of acute nephritis in which there was cardiac involvement. He concluded that, in the absence of disease of the valves or coronary arteries or any other demonstrable cardiac pathologic change, the sudden appearance of cardiac decompensation, with dilatation of the right side of the heart, pulmonary congestion, and an enlarged liver, should make one suspect that acute nephritis is present. Levy was of the opinion that edema in some of these cases of nephritis may be attributed, at least in part, to circulatory failure.

Since then, there have been a number of interesting studies of the heart in acute glomerulonephritis. Guthrie[11] observed that the left ventricle was hypertrophied in a third of thirty-four cases of acute nephritis. Master, Jaffe, and Dack[12, 13] studied thirty cases of acute glomerulonephritis with particular reference to the electrocardiographic changes. They were able to show a direct correlation between the electrocardiographic changes and the clinical and laboratory evidence of cardiovascular involvement. They concluded that in acute nephritis there is involvement of the heart, probably as a part of a general vascular disturbance. In their cases the electrocardiographic changes frequently lasted longer than the symptoms. They noted changes in the T waves similar to those which occur in occlusion of the anterior descending branch of the left coronary artery.

Langendorf and Pick[14] made serial electrocardiographic studies in twelve cases of acute glomerulonephritis. Among other changes, they noted flattening or inversion of T_1 and inversion of T_4. They distinguished these abnormalities from those caused by infarction of the anterior wall of the left ventricle by the absence of changes in the S-T segment and Q wave, so frequently found in acute infarction of the myocardium. The absence of an elevation of the S-T segment in the early tracings in acute nephritis helped to obviate the confusion with alterations produced by acute pericarditis.

In 71 per cent of the cases of acute nephritis reported by Whitehall, Longcope, and Williams[15] there was cardiac failure which was in many

instances out of proportion to the severity of the nephritis. In a subsequent study, Williams[16] was unable to establish any correlation between the electrocardiographic changes and the signs of cardiac or renal insufficiency.

By means of electrocardiographic and teleroentgenographic studies, Hayman and Martin[17] were able to find evidences of myocardial damage in half of their cases of acute nephritis.

Feller and Hurevitz[18] reported two cases of acute nephritis accompanied by cardiac failure which was predominantly left ventricular. They found that cardiac decompensation may occur early in the disease, even before clinical evidence of renal damage. They were of the opinion that many of these patients have panarteriolitis, with involvement of the vessels of the myocardium.

Rubin and Rapoport[19] observed that the most frequent complication in acute hemorrhagic nephritis is cardiac, and that many patients who die in the acute attack die of cardiac failure. Of their series of fifty-five cases, severe myocardial damage was encountered in fourteen, in twelve of which there was definite cardiac decompensation. The clinical evidences of cardiac involvement and failure in these cases were dyspnea, cardiac enlargement found by physical examination and in teleroentgenograms, muffled heart tones, tachycardia, mitral systolic murmurs, gallop rhythm, enlarged and tender liver, venous engorgement, pulmonary and peripheral edema, and electrocardiographic changes indicating some degree of myocardial damage. They expressed the belief that the two factors in the acute phase of nephritis which may affect the heart adversely are myocardial damage and hypertension. Although Rubin and Rapoport observed that cardiac damage was a definite danger to life in the acute phase of glomerulonephritis, in their opinion the ultimate cardiac prognosis is good.

REPORT OF CASES

We have reviewed data on one hundred thirty-six cases of acute glomerulonephritis at the Mayo Clinic with particular reference to the cardiac complications. In twenty-two cases (16 per cent) there were obvious cardiac manifestations of varying severity. In no case was there evidence of any other etiological factor, such as rheumatic, syphilitic, or coronary heart disease, previous hypertension, or hyperthyroidism. In addition, in twelve cases (9 per cent) some cardiac involvement, probably related to the acute glomerulonephritis, was observed at necropsy, but these cases were not included because some other factor, such as coronary sclerosis, low-grade hypertension, or hyperthyroidism, was present. Fortunately, the mortality rate of acute glomerulonephritis is low, and, consequently, most of the cardiac manifestations will be those observed on clinical rather than post-mortem examination. The incidence of cardiac complications in the present

series of cases of acute glomerulonephritis is undoubtedly too low because not all of the patients were under observation from the onset of their illness. Several patients reported symptoms or signs of cardiac involvement that had occurred earlier in the course of their disease, but, since all evidences of cardiac involvement had disappeared prior to examination at the clinic, these cases were not included in the present series. If serial electrocardiograms had been taken routinely in every case of acute glomerulonephritis, the percentage of cases in which there was evidence of involvement of the heart undoubtedly would have been increased.

The following brief summaries of nine cases illustrate various cardiac complications in acute glomerulonephritis.

CASE 1.—A boy, 15 years of age, was admitted to the clinic March 9, 1939, acutely ill and stuporous. Infection of the upper part of the respiratory tract had begun February 25. On March 5, a severe headache had developed and the patient had noticed dark brown urine. On March 7, he had had chills and fever and had become mentally confused. The heart was normal to physical examination except for tachycardia and a soft, systolic murmur at the apex. The blood pressure was 160/65. Routine urinalysis showed gross blood, many granular casts, and albuminuria grade 4 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition). The concentration of urea was 92 mg. per 100 c.c. of blood. A culture of the spinal fluid was positive for Type XII pneumococcus. The clinical diagnosis was pneumococcic meningitis, with acute glomerulonephritis, hypertension, and uremia. After sulfapyridine therapy the patient improved temporarily, and the culture of his spinal fluid became negative. However, on March 15, 1939, a relapse occurred, and he died March 29. At necropsy the heart weighed 205 grams, and there was pronounced dilatation of the left auricle and ventricle. The surface of both kidneys was covered with numerous red dots. Histologic examination of the kidneys revealed such extreme swelling of the endothelial cells of the glomeruli that the capillaries of the glomerular tufts were practically obliterated. Some of the tubules contained blood and necrotic cellular debris.

CASE 2.—The patient was a woman, 30 years of age. On Dec. 6, 1930, a "cold" and a discharge from the left ear developed. On December 24, she suddenly had an attack of dyspnea, followed by a similar attack the next day. Morphine and epinephrine did not give any relief. On December 27, she had a very severe attack of dyspnea, and died of severe pulmonary congestion several hours after hospitalization elsewhere. At necropsy the pericardial cavity was found to contain 150 c.c. of clear fluid. The heart weighed 250 grams. The left ventricle was greatly dilated, but there were no other gross cardiac abnormalities. The right pleural cavity contained 1,000 c.c. of fluid, and the left pleural cavity contained 1,500 c.c. The liver extended 8 cm. below the costal margin in the midclavicular line and was moderately congested. The kidneys were congested, and histologic examination revealed large, very cellular glomeruli containing many polymorphonuclear cells within their capillaries, but very few erythrocytes. The proximal convoluted tubules showed degeneration, with some very pale nuclei and granular cytoplasm. There was severe congestion of the small blood vessels in the medulla.

CASE 3.—A man, 21 years of age, was admitted to the clinic Aug. 18, 1939, suffering from severe peripheral edema. He had been well until August 8, when he began to notice shortness of breath on exertion. On August 13 a nonproductive cough and

nocturnal dyspnea had developed, but he was able to continue working. Three days later he was unable to wear his shoes because of peripheral edema.

On physical examination, the patient weighed 275 pounds (124.7 kg.). The pharynx was injected and the tonsils were grossly infected. Severe dyspnea was noted and there was moderate edema of the ankles. Râles were heard at the bases of both lungs, and the heart was greatly enlarged to the left to percussion. There were no murmurs. The blood pressure was 160/98. Urinalysis showed albuminuria, grade 2 (on the basis of 1 to 4), gross blood, and granular casts. The concentration of hemoglobin was 10.8 Gm. per 100 c.c. of blood (71 per cent); the erythrocytes numbered 3,770,000, and the leucocytes, 6,000, in each cubic millimeter of blood. The concentration of urea was 62 mg. per 100 c.c. of blood. Roentgenographic examination of the chest revealed pronounced cardiac enlargement. The electrocardiogram showed a rate of 103, and slurred QRS, diphasic P waves, and inverted T waves in Lead III.

The diagnosis was acute glomerulonephritis with cardiac decompensation. The patient responded satisfactorily to treatment and was dismissed from the hospital Sept. 7, 1939. He was seen again on Oct. 24, 1939, at which time the results of routine urinalysis were normal except for an occasional erythrocyte. His blood pressure was 124/84, and his pulse rate, 68; clinical examination of the heart did not reveal any evidence of organic disease.

CASE 4.—A girl, 3 years of age, was admitted to the clinic Aug. 7, 1939, with albuminuria, grade 2, hyaline and granular casts in the urine, and gross hematuria. Four weeks prior to admission she had had a head cold and a temperature of 100° to 104° F. for five days. Two weeks prior to admission she had impetigo, followed by a skin eruption on the trunk and face, with a temperature of 103° to 104° F. One week prior to admission gross hematuria was noted.

Physical examination revealed enlargement of the heart to the left and a loud systolic murmur over the precordium which was transmitted to the axilla. The blood pressure was 100/40. The patient returned to the clinic in November, 1939, at which time the results of urinalysis were negative. The heart had decreased noticeably in size on physical examination, and the systolic murmur had decreased in intensity and was inconstant.

CASE 5.—A boy, 4 years of age, was admitted to the clinic March 23, 1940. He had a loud systolic murmur over the entire precordium. One month prior to admission he had had an infection of the upper part of the respiratory tract. Three weeks prior to admission gross hematuria was noted. The hematuria lasted three days and disappeared. One week prior to admission the infection of the upper part of the respiratory tract recurred. Coincident with this, a loud systolic murmur appeared and became audible over the entire precordium. Gross hematuria again was noted.

Physical examination revealed a pulse rate of 120. Albuminuria was graded 2, and the urine contained hyaline and granular casts and gross blood. The concentration of urea was 40 mg. per 100 c.c. of blood. Five days after admission the results of routine urinalysis were negative. The cardiac murmur completely disappeared and the cardiac rate decreased to 90 beats per minute.

CASE 6.—A man, 55 years of age, registered at the clinic Jan. 25, 1939. Two weeks prior to admission he had had influenza, and his temperature had been 103° F. Eleven days prior to admission otitis media developed on the left side. The eardrum ruptured spontaneously and the ear drained freely. Twenty-four hours prior to admission he had a chill, a temperature of 103° F., sore throat, and gross hematuria.

Physical examination revealed a loud systolic murmur diffusely over the precordium, but most intense at the aortic area. Albuminuria was graded 3, and gross blood was found in the urine. The concentration of urea was 26 mg. per 100 c.c. of blood. The patient was seen again in November, 1939, when clinical examination of his heart gave entirely negative results except for a slight accentuation of the aortic second sound.

CASE 7.—A boy, 11 years of age, was admitted to the clinic April 21, 1939, in a stuporous condition. He had been well until March 25 when he developed an acute sore throat which lasted three days. Enlarged, tender, cervical lymph nodes persisted. On April 12 gross hematuria was noted. Twenty-four hours prior to admission a severe headache developed and the patient became comatose. Physical examination revealed that the cardiac apex was 1.5 cm. to the left of the midclavicular line. The blood pressure was 160/110. Urinalysis revealed albuminuria, grade 4, granular casts, and gross blood. The concentration of urea was 52 mg. per 100 c.c. of blood. Roentgenographic examination of the thorax revealed slight cardiac enlargement and congestion of both hilar regions. When the patient was dismissed two weeks later, all signs of pulmonary congestion had disappeared, and the heart was found to be definitely smaller than at the previous examination.

CASE 8.—A boy, 17 years of age, was admitted to the clinic Jan. 22, 1939. He had been well until Dec. 20, 1938, when tonsillitis and a peritonsillar abscess developed. On Jan. 7, 1939, the abscess opened spontaneously and he felt much better. On January 10 swelling of the face and headaches appeared. Twenty-four hours prior to admission severe headaches and generalized convulsions occurred.

Physical examination revealed a loud systolic murmur at the apex. The pulmonic second sound was much louder than the aortic second sound. Râles were heard at the bases of both lungs. The blood pressure was 130/90. The urinalysis revealed albuminuria, grade 4, hyaline and granular casts, and gross blood. The concentration of urea was 26 mg. per 100 c.c. of blood. Five days after admission all signs of pulmonary congestion had disappeared completely.

CASE 9.—A girl, 10 years of age, was admitted to the clinic Jan. 13, 1939. Four weeks prior to admission she had had measles. Three weeks prior to admission a discharge from both ears developed. Physical examination revealed an extrasystole every fourth beat. Râles were heard at the bases of both lungs. Urinalysis revealed albuminuria, grade 3, granular casts, and gross blood. The concentration of urea was 94 mg. per 100 c.c. of blood. Roentgenographic examination of the thorax revealed congestion at the right hilum and right cardiophrenic angle. All signs referable to involvement of the heart disappeared completely within two weeks after admission.

COMMENT

The primary cause of death in the first case was pneumococcic meningitis, but severe dilatation of the heart may have been an important contributory factor. The only explanation for the death of the second patient was cardiac dilatation and anasarca. This case also illustrates how acute and fulminating the cardiac complication may be. In the third case, the symptoms that brought the patient to the clinic were those of cardiac decompensation, and so predominant were the cardiac symptoms that it was not until routine urinalysis was done that acute glomerulonephritis was even suspected. The possibility that renal congestion might have been secondary to cardiac congestion in this case

was considered unlikely because of the absence of any cardiac lesion before or after the patient's examination at the clinic. The hypertension was transient and coincided with the onset of the acute illness. There was no antecedent history of rheumatic fever or valvular heart disease. This case also emphasizes the importance of considering acute glomerulonephritis in every case of myocardial failure in which there is no other demonstrable evidence of cardiac disease. In contrast to the second case, the third case illustrates how rapidly the severe congestive failure may improve, leaving no residual sign of heart disease.

Cases 4, 5, and 6 illustrate minor cardiac complications, such as murmurs and slight dilatation, that disappear completely when the acute illness subsides. There were no signs of congestive failure in these three cases. In Cases 7, 8, and 9 there were also dilatation of the heart and murmurs that disappeared subsequently, but, in addition, the condition was complicated by mild pulmonary congestion.

In this series of cases no direct correlation between the severity of the nephritis and the incidence or severity of the cardiac involvement could be found. Although in most cases there was some elevation of the systemic blood pressure, there was no significant relation between such transient hypertension and involvement of the heart.

SUMMARY

Cardiac complications are fairly frequent in cases of acute glomerulonephritis, and patients who die during the acute phase may die from heart failure. Evidence of obvious cardiac involvement was observed in 16 per cent of 136 cases. The cardiac complications varied from murmurs, with or without dilatation, to manifestations of pulmonary congestion or severe cardiac decompensation. In cases in which congestive heart failure is a complicating factor, the patient may die suddenly or may improve rapidly, leaving no demonstrable evidence of organic heart disease. The hearts of patients who die from cardiac decompensation ofen show great dilatation, with or without hypertrophy, but dilatation usually dominates the picture. Signs of cardiac involvement may appear and disappear rapidly, and there is no apparent correlation between the severity of the nephritis, the height of the blood pressure, and the incidence or severity of the cardiac complications.

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THE PRESSOR ACTION OF PAREDRINE; FURTHER OBSERVATIONS

ARNOLD IGLAUER, M.D., AND WILLIAM E. MOLLE, M.D.
CINCINNATI, OHIO

SEVERAL studies have been made of the pressor action of paredrine (p-hydroxy-a-methyl-phenylethylamine hydrobromide) on normal human subjects.[1-5] The therapeutic effect of this compound on vasomotor collapse of various kinds has also been investigated.[3, 6, 7] In certain types of lowered blood pressure, such as that during spinal anesthesia, the administration of 5 to 10 mg. of paredrine parenterally usually produces an adequate and prolonged blood pressure increase.[7] However, in the shocklike state which may occur with severe infections, paredrine and the closely related compound, paredrinol (N-methyl paredrine), frequently fail to produce the anticipated pressor response.[3, 8] The effect of paredrine on the cardiovascular systems of patients with infection, but no shock, has not been previously reported. In the present study, paredrine was administered to hospital patients with various infections, but with none of the manifestations of vasomotor collapse. Cardiac irregularities were noted in some subjects after the injection of paredrine; since only one brief comment on the production of arrhythmia by paredrine[1] was found in the literature, electrocardiograms were made during many of the experiments.

METHODS

Paredrine* was administered twenty-one times to twenty patients who were on the wards of the Cincinnati General Hospital because of various infections; none showed any evidence of shock at the time the study was made. One of these patients, however, subsequently developed vasomotor collapse, and was given paredrine.

Five additional patients were studied before and during fever produced by malarial inoculation or the injection of typhoid vaccine. To ascertain the constancy of response to paredrine in a given patient, the same dose was repeated in six patients whose clinical status remained unchanged; the intervals between injections ranged from one hour to seven days. Five of these subjects were free of acute infection, and were considered normal controls. None of the twenty-eight subjects showed any evidence of cardiovascular disease.

Three-lead electrocardiograms were made with an amplifier type of electrocardiograph on thirteen of the patients before, and at intervals after, the administration of paredrine.

All procedures were carried out at the bedside, with the patient recumbent. Blood pressure was measured at one- to two-minute intervals by the auscultatory

From the Cardiac Laboratory and Department of Internal Medicine, University of Cincinnati, College of Medicine.

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TABLE I

RESPONSE TO PAREDRINE OF PATIENTS WHO RECEIVED REPEATED INJECTIONS

NO.	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DEGREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. INCREASE (MM. HG)	DURATION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
1	3/ 2/42	F	16	72	6	99	Tuberculous peritonitis	94/66	31/20	41	125/ 86
	3/ 2/42				6	99		92/66	38/34	52	130/100
2	5/25/42	M	46	150	10	98.6	General paresis	120/90	96/28	32	216/118
	5/31/42				10	98.6		118/82	122/48	43	240/130
3	5/31/42	M	37	130	8	97.6	Syphilitic meningitis	94/60	58/34	25	152/ 94
	5/31/42				8	97.6		94/60	56/34	43	150/ 94
4	6/14/42	M	29	140	10	98.6	Syphilis of central nervous system	126/84	64/21	30	190/105
	6/21/42				10	98.6		120/78	70/32	32	190/110
5	6/15/42	M	37	125	8	98.6	Convalescent	116/68	49/17	35	165/ 85
	6/15/42				8	98.6		112/64	48/16	46	160/ 80
6	6/21/42	M	29	145	10	98.6	Convalescent	114/68	82/32	60+	196/100
	6/21/42				10	98.6		106/64	84/46	65+	190/110

method; a standard 13 cm. arm cuff was used. Paredrine was given intravenously in a dose of approximately 1 mg. per 7 kg. after the pulse rate and blood pressure reached a constant, low level. The intravenous administration of paredrine to normal subjects in approximately the dosage used in the present study has been previously reported to produce a rise in systolic blood pressure varying from 28 to 98 mm.; diastolic blood pressure increases varying from 10 to 56 mm. were noted, and the blood pressure was found to return to the initial level in from 20 to 70 minutes.[2, 4]

In the construction of the tables, the maximal systolic and diastolic pressures which were attained were used in computing the response, although in many experiments the two pressures did not reach peak levels simultaneously. The results obtained in several of the experiments have been included in more than one table.

OBSERVATIONS

The intravenous injection of paredrine usually produced no symptoms. A few patients noted palpitation, usually in association with a clinically discernible arrhythmia. Many of the patients observed forceful heart action, and several noted rather disagreeable throbbing in the temporal region. Several patients complained of dyspnea of three to four minutes' duration, although there was no consistent change in the depth or rate of respiration. The highest blood pressure level occurred one to four minutes after injection of the drug, and the cardiac rate was definitely decreased in all but one of the patients who showed a good pressor response.

Repeated Injections.—The blood pressure response to the intravenous injection of a given dose of paredrine was fairly constant (Table I). The maximum difference in systolic pressures was noted in Case 2; the increase was 96 mm. of mercury after the first injection of 10 mg., as compared with 122 mm. after the second injection of the same amount. The diastolic pressure increase was more variable than the systolic increase, perhaps because difficulty was frequently experienced in ascertaining the exact point of change of the arterial sounds. The duration of the pressor response in the same patient was somewhat variable.

In the five subjects (Cases 2 to 6) who were used as controls, the greatest increase in systolic pressure was 122 mm., and the least increase, 48 mm. The increase in diastolic pressure varied from 16 to 48 mm. The increase in blood pressure persisted from 25 to 65 minutes.

Infections.—The nine patients with miscellaneous infections and no signs of shock showed increases in systolic and diastolic blood pressure and a duration of change which did not differ significantly from the normal range (Table II). The systolic pressure increase varied from 34 to 74 mm., the diastolic increase, from 9 to 38 mm., and the duration of the rise, from 24 to 45 minutes. Patients 7, 8, and 10 were receiving drugs of the sulfonamide group at the time the tests were made. Eleven of the patients had tuberculous infections; they received somewhat higher doses of paredrine per kilogram of body weight than the other patients (Table III). In five of the tuberculous patients, the duration of blood pressure change was twenty minutes or less (Cases

TABLE II

RESPONSE TO PAREDRINE OF PATIENTS WITH INFECTIONS

(NONTUBERCULOUS INFECTIONS)

CASE	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DEGREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. INCREASE (MM. HG)	DURATION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
7	11/17/41	F	18	95	6	99	Pyelitis	106/68	62/22	28	168/90
8	12/14/41	F	21	120	8	98.4	Pyelitis	102/86	53/ 9	45	155/95
9	12/14/42	F	39	125	10	99.8	Rheumatoid arthritis	106/74	74/36	40	180/110
10	12/21/41	F	30	175	8	99	Gonorrheal arthritis	122/78	54/12	34	176/90
11	12/23/41	F	58	118	8	101.8	Tularemia	104/62	50/23	33	154/85
12	12/28/41	F	28	183	10	100	Gonorrheal arthritis	116/64	34/16	25	150/80
13	1/12/42	M	38	110	8	105	Paresis and malaria	104/56	66/38	24	170/94
14	3/ 2/42	F	57	138	10	99	Pneumonia	126/70	38/24	33	164/94
15	4/12/42	F	53	90	8	98.6	Rheumatoid arthritis	108/68	56/20	29	164/88

TABLE III

RESPONSE TO PAREDRINE OF PATIENTS WITH INFECTIONS

(TUBERCULOUS INFECTIONS)

NO.	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DEGREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. INCREASE (MM. HG)	DURATION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
1	3/ 2/42	F	16	72	6	99	Tuberculous peritonitis	94/66	31/20	41	125/ 86
	3/ 2/42				6			92/66	38/34	52	130/100
16	12/ 3/41	F	25	85	8	99.8	Pulmonary tuberculosis	86/58	42/34	20	128/ 92
17	12/ 8/42	F	30	90	8	98	Pulmonary tuberculosis	76/58	20/12	20	96/ 70
18	12/26/41	F	29	112	8	98.6	Psoas abscess	125/84	65/16	45	190/100
19	1/24/42	M	46	100	8	102	Pulmonary tuberculosis	108/66	26/18	12	134/ 84
20	2/ 8/42	F	17	120	8	101.8	Pleurisy with effusion	100/66	58/34	13	158/100
21	3/30/42	F	14	86	10	98	Pleurisy with effusion	114/70	42/28	37	156/ 98
22	3/30/42	M	19	104	10	98	Tuberculous peritonitis	108/88	22/12	15	130/100
23	4/19/42	F	34	120	10	98	Pleurisy with effusion	98/72	106/28	40	204/100
24	4/30/42	M	37	135	8	100.6	Pulmonary tuberculosis	114/82	86/23	36	200/105
25	5/24/42	M	41	135	10	98	Pulmonary tuberculosis	116/70	40/15	37	156/ 85

TABLE IV

RESPONSE TO PAREDRINE BEFORE AND DURING FEVER

CASE	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DEGREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. INCREASE (MM. HG)	DURATION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
9	12/14/42	F	39	125	10	99.8	Rheumatoid arthritis	106/74	74/36	40	180/110
	12/15/42				10	103.6	After typhoid vaccine	94/58	50/36	31	144/94
10	12/21/41	F	30	175	8	99	Gonorrheal arthritis	122/78	54/12	34	176/90
	12/27/41				8	106	After typhoid vaccine	124/70	26/10	10	150/80
12	12/28/41	F	28	183	10	100	Gonorrheal arthritis	116/64	34/16	25	150/80
	12/29/41				10	103.5	After typhoid vaccine	96/60	64/26	29	160/86
26	12/21/41	M	43	129	8	98.6	Syphilis of central nervous system	86/44	68/22	70	154/66
	12/23/41				8	102	After typhoid vaccine	106/54	36/14	36	142/68
27	4/30/42	M	57	125	8	98.6	Syphilis of central nervous system	112/76	48/18	29	160/94
	5/24/42				8	105	After malarial chill	120/68	28/ 8	21	148/76
	5/25/42				8	98.8		102/70	38/18	23	140/88

16, 17, 19, 20, 22). In three of the five, the increase in systolic pressure was less than 30 mm. (Cases 17, 19, 22). The initial heart rate in all five patients was more than 100 beats per minute, and these were the only cases in which the pulse rate increased after injection of paredrine. In three of the remaining tuberculous patients, the systolic blood pressure increase was less than the smallest increase observed in the control series, i.e., 48 mm. (Cases 1, 21, 25). Three of the tuberculous patients showed a marked pressor response to the intravenous injection of paredrine (Cases 18, 23, 24).

Fever.—In two of the patients with fever produced by typhoid vaccine (Cases 9, 10, Table IV), the injection of paredrine produced a smaller rise in systolic pressure than during an afebrile period. The duration of the blood pressure elevation was shorter in both of these patients during fever. In a third patient (Case 26) the response was less after a chill than in the control period, but a higher initial pressure made the change somewhat difficult to interpret. In Case 27, the response of the blood pressure to the injection of paredrine was less in the febrile period after a malarial chill than it had been before inoculation with malaria, but did not differ strikingly from the response on the subsequent day, after the temperature had returned to normal. In one patient (Case 12), paredrine produced a greater rise in blood pressure during fever produced by typhoid vaccine than in the pretreatment trial.

Electrocardiographic Observations.—Increase in the height of the T wave in one or more leads was observed in eleven patients (Cases 1, 2, 3, 4, 5, 6, 15, 21, 23, 24, 27). Only three of the thirteen patients whose electrocardiograms were studied failed to show a change in P waves or P-R interval (Cases 3, 22, 27). In two of these a good pressor response to paredrine occurred (Cases 3, 27), but the blood pressure increase in Case 22 was small. In two patients (Cases 1 and 6, Fig. 1), the site of impulse formation changed so frequently that a diagnosis of wandering pacemaker seemed justified, although the ventricular rhythm remained fairly regular in one (Case 6). In one subject (Case 4, Fig. 2), the injection of paredrine was followed by a gross irregularity, with impulse formation shifting between the auricle, A-V node, and ventricle. In three patients (Cases 21, 23, and 28), inversion of the P waves in one or more leads, with shortening of the P-R interval to 0.12 second or less, was noted (Fig. 3). These patients were thought to have auriculoventricular nodal rhythm. In three of the remaining patients, a change in the duration of the P-R interval (Case 2), or less change in both P-R interval and P wave (Cases 5 and 24), was noted. It was felt that these changes were probably due to ectopic impulse formation. The maximum duration of the arrhythmia in any of the above cases was thirty-five minutes. T-wave changes usually persisted until blood pressure and pulse rate returned to the control level.

In Case 15 (Fig. 4) there appeared to be a spontaneous variation in the form of the P wave. On April 12, the patient's control electro-

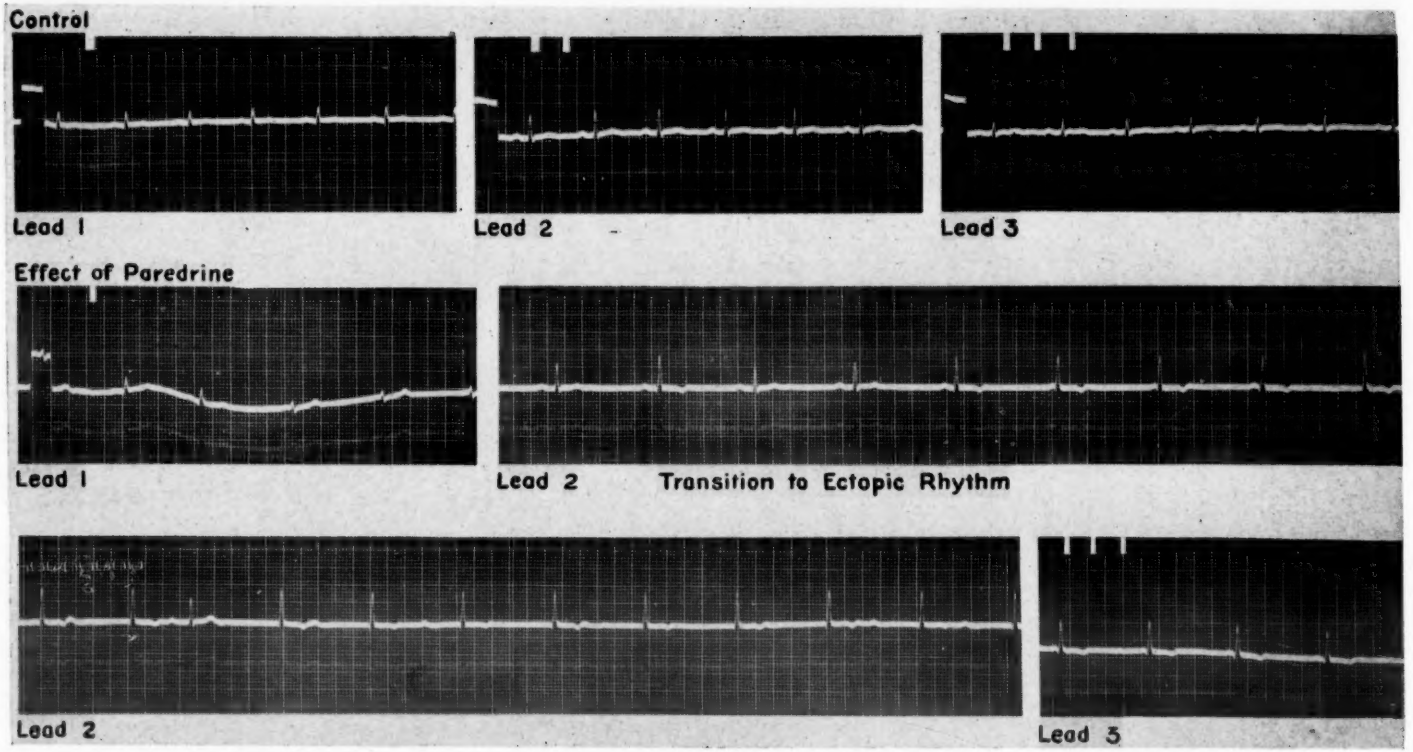

Fig. 1.—Case 6. Wandering pacemaker (possibly parasystole) after intravenous injection of 10 mg. of paredrine, B. P. 190/110. Leads I and II, several minutes after injection of paredrine, show alternation between sinus rhythm and an ectopic rhythm with changed QRS complexes and T waves. The QRS complexes in Lead II show no constant time relation to the P waves, which occur at irregular intervals. The ventricular rate decreases markedly, but remains almost regular. Lead III shows nodal rhythm with a very short P-R interval and ventricular complexes differing from the control tracing. A tracing (not illustrated), taken nineteen minutes after the injection of the drug, showed return to sinus rhythm, with QRS complexes resembling the control, but with higher T waves in all leads. The T waves in the electrocardiogram taken after sixty minutes were the same as in the control strip.

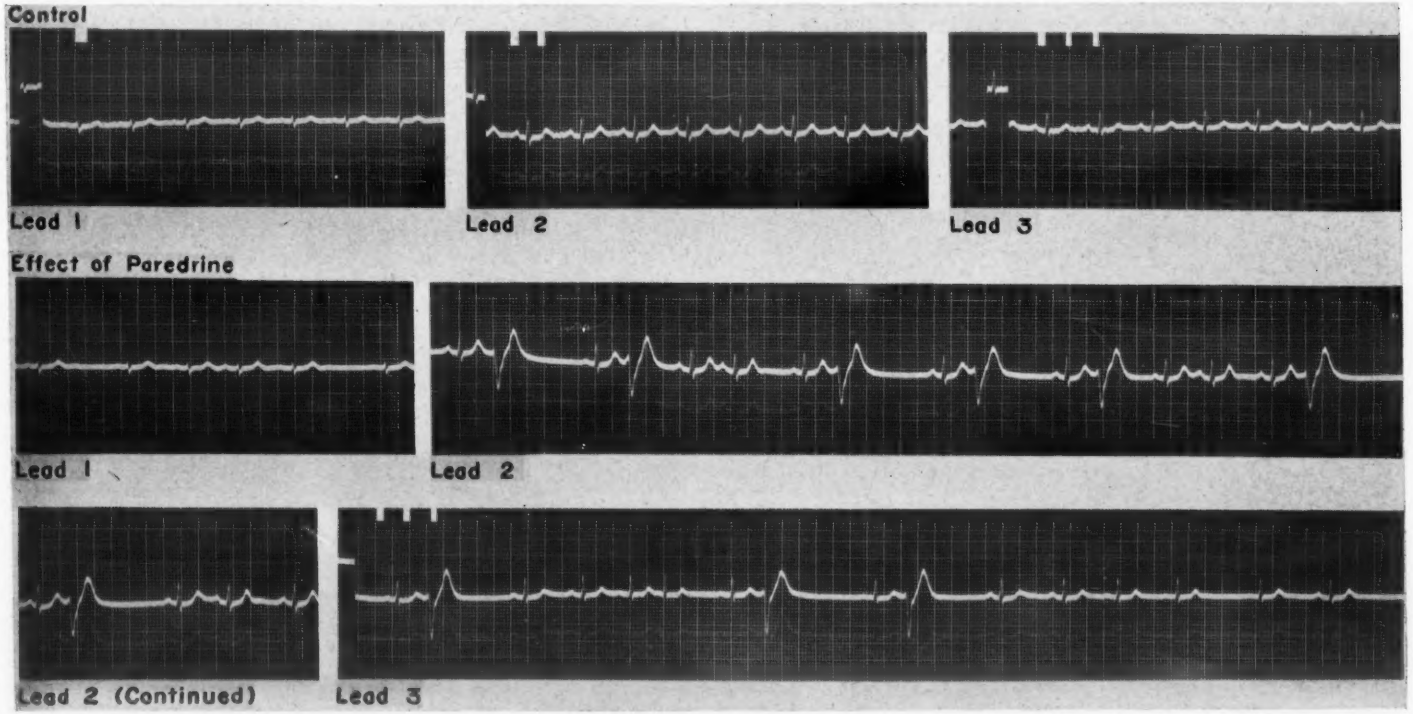

Fig. 2.—Case 4. Grossly irregular rhythm after 10 mg. of paredrine, B. P. 190/105.
Leads I, II, and III, taken three minutes after injection of paredrine, show extrasystoles from multiple foci—auricular, nodal, and ventricular. The T waves of the sinus beats are somewhat higher in all three leads. A tracing (not illustrated), taken sixteen minutes after giving the drug, showed sinus rhythm with high T waves. The tracing taken sixty minutes after giving paredrine was identical with the control.

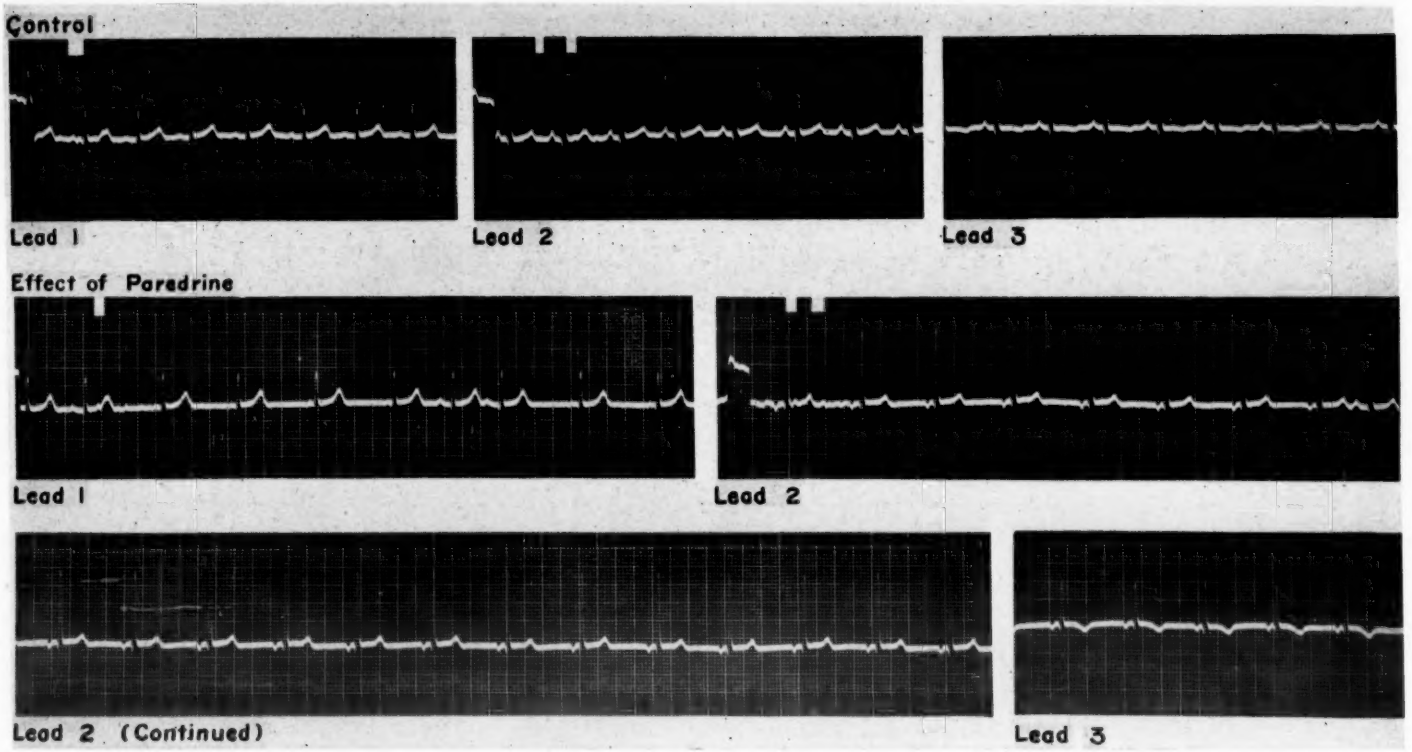

Fig. 3.—Case 21. Auriculoventricular nodal rhythm after 10 mg. of paredrine, B. P. 156/98.
Control strips show upright P waves, with P-R interval of 0.16 second. In Lead I, taken three minutes after injecting paredrine, most of the complexes show a diphasic P wave, with P-R interval of 0.10 second. In Lead II all complexes except one show a sharply inverted P wave, with P-R interval shortened to 0.10 second. Lead III also shows inverted P wave and short P-R interval. The QRS complexes are not changed after paredrine: T_1 is higher, T_2 unchanged, and T_3 more sharply inverted. The electrocardiogram and blood pressure returned to normal in thirty-five minutes.

cardiogram showed low P waves, with a P-R interval of 0.12 second. The intravenous administration of paredrine produced a marked increase in the height, and a change in the shape, of the P wave in Leads II and III; these persisted for several hours. By the following day, the tracing had resumed its original form. On April 17, before the administration of any drug, the electrocardiogram showed P waves

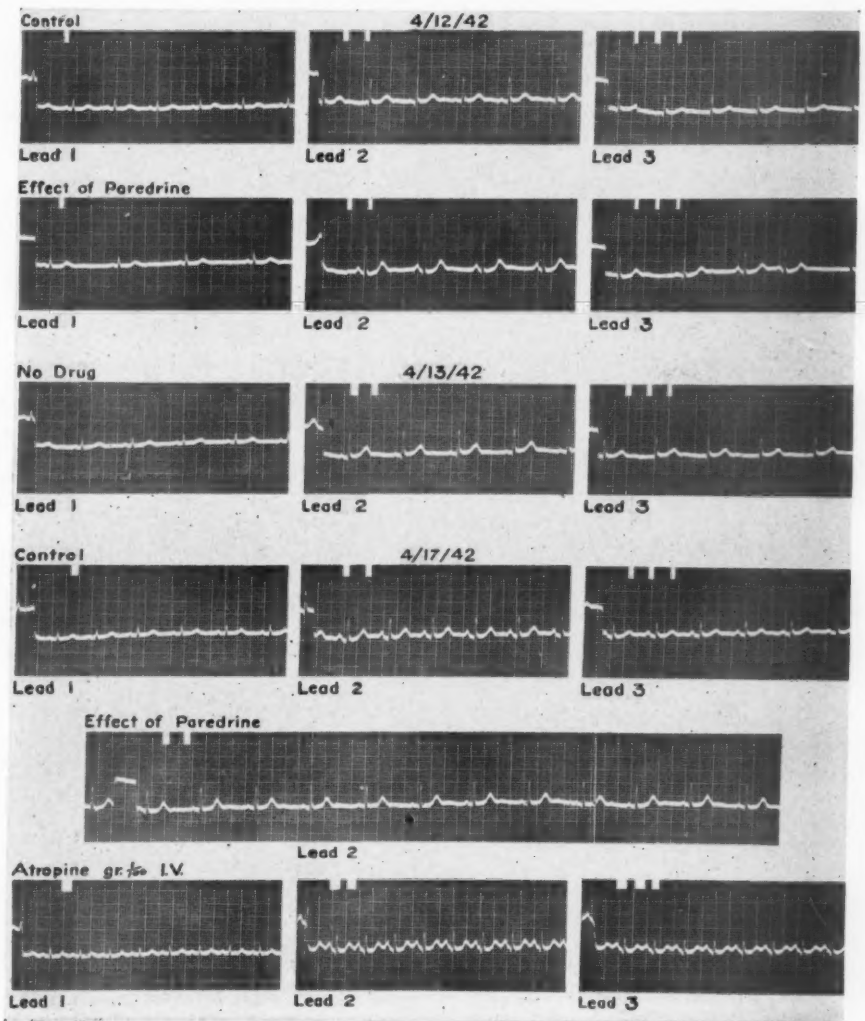

Fig. 4.—Case 15. Changes in P waves spontaneously and after injection of paredrine and atropine.

Control tracing on April 12, 1942 shows rather low P waves in all leads, P-R interval 0.12 second. After injection of 8 mg. of paredrine intravenously (B. P. 164/88), the P waves become higher. Lead III shows examples of both types of P wave. By the next day (April 13) the electrocardiogram had resumed its original form. The control tracing of April 17 appears identical with the tracing obtained after paredrine in the previous experiment. After injection of paredrine, low P waves are noted in Lead II. A moment later, after injection of atropine, the P waves again become high. An electrocardiogram taken three days later (not illustrated) showed high P waves with P-R interval of 0.14 second.

TABLE V

CASE	DATE	SEX	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DEGREES F.)	DIAGNOSIS	INIT. B.P. (MM. HG)	PEAK B.P. (MM. HG)	INITIAL PULSE RATE PER MINUTE	PULSE RATE AT PEAK B.P. PER MINUTE	ALTERATION IN ELECTROCARDIOGRAM AFTER PAREDRINE
1	3/ 2/42	F	72	6	99	Tuberculous peritonitis	92/66	130/100	120	75	Wandering pacemaker. QRS complex unchanged, T waves higher. Return to initial form in 20 min.
2	5/25/42	M	150	10	98.6	General paresis	120/90	216/118	68	57	P-R interval shortened from 0.18 to 0.12 sec., without change in form of P wave or QRS complex. T waves higher, Leads I, II, III. Rhythm regular. Return to initial form in 17 min.
3	5/31/42	M	130	8	97.6	Syphilis of central nervous system	94/60	150/ 94	94	70	Decrease in rate only significant change
4	6/14/42	M	140	10	98.6	Syphilis of central nervous system	126/84	190/105	95	Irregular	Grossly irregular rhythm with beats from varying foci (see Fig. 2)
5	6/15/42	M	125	8	98.6	Pneumonia (convalescent)	116/68	165/ 85	90	60	Regular ventricular rhythm, with higher P waves, and P-R interval changed from 0.16 to 0.12 sec. QRS complex unchanged, T waves higher. Rhythm normal in 18 min., T waves at initial level in 40 min.
6	6/21/42	M	145	10	98.6	Gonorrheal arthritis (convalescent)	106/64	190/110	75	60	Nodal rhythm with marked variation in P-R interval (see Fig. 1)

15	4/12/42	F	90	8	98.6	Rheumatoid arthritis	108/68	164/ 88	90	60	Variation in form of P waves after paredrine and spontaneously (see Fig. 4 and discussion in text)
21	3/30/42	F	86	10	98	Pleurisy with effusion	114/70	156/ 98	100	75	Inversion of P in all three leads, with shortening of P-R interval from 0.16 to 0.10 sec. (see Fig. 3)
22	3/30/42	M	104	10	98	Tuberculous peritonitis	108/88	130/100	120	136	Increase in rate only definite change
23	4/19/42	F	120	10	98	Pleurisy with effusion	98/72	204/100	86	55	Inversion of P wave in Leads II and III, with shortening of P-R interval from 0.16 to 0.12 sec. Slight arrhythmia due to irregular occurrence of complexes with upright P waves. QRS unchanged, T_2 and T_3 higher. Return to initial form in 35 min.
24	4/30/42	M	135	8	100.6	Pulmonary tuberculosis	114/82	200/105	96	80	P waves much higher in Leads II and III, with shortening of P-R interval from 0.16 to 0.13 sec. Increased amplitude of QRS complex and T waves. Return to initial form in 30 min.
27	4/30/42	M	125	8	98.6	Syphilis of central nervous system	112/76	160/ 94	84	84	T waves higher in all three leads. QRS complexes and rate unchanged
28	4/ 4/42	F	90	8	100	Cancer of cervix uteri	118/84	178/110	100	80	Change in form of P_1 and P_2, inversion of P_3. P-R interval shortened from 0.15 to 0.12 sec. QRS complexes unchanged, T waves higher. Return to initial form in 15 min.

identical with those on April 12 after the administration of paredrine. A few minutes after the injection of 6 mg. of paredrine, the P waves again appeared low, as they had in the first electrocardiogram, sixteen days before. Atropine ($\frac{1}{100}$ grain) was given intravenously while the blood pressure remained elevated, and, after about one minute, the P waves returned to the high form. The P-R interval remained at 0.12 second throughout both these experiments. An electrocardiogram three days later showed high P waves, with a P-R interval of 0.14 second.

DISCUSSION

The present study confirms previous observations that the injection of paredrine usually produces no discomfort. The moderate respiratory distress which occurred in some of our patients has not been noted previously. The constant response of normal subjects to the same amount of the drug is at variance with the observations of Kunkel, Stead, and Weiss;[8] these authors found that the pressor response after the intramuscular injection of paredrinol was quite variable in the same subject. The increase in blood pressure in the control group and in the majority of the ill patients agreed fairly well with the results of previous investigations of the effect of the intravenous injection of paredrine.[2, 4]

The adequate and prolonged pressor response to the injection of paredrine in the course of acute infections indicates that a decreased response to paredrine in medical shock is not dependent on the presence of infection alone. This is borne out by observations made in Case 11. This patient showed a marked pressor response to the intravenous injection of paredrine when her blood pressure was normal. Seventeen days later, when her blood pressure had dropped to 50/20 and signs of shock were present, the intravenous injection of 20 mg. of paredrine produced a brief elevation of blood pressure to 110/60, but subsequent, large doses had little effect. Kunkel, et al.,[8] observed a similar "tachyphylactic" response to paredrinol in medical shock. The present study failed to suggest a reason for the diminished response to paredrine in shocklike states associated with severe infections, nor did it help to explain the mechanism of the vasomotor collapse.

The relatively small pressor response to the injection of paredrine in some of the tuberculous patients was quite clear-cut. In general, the least response was observed in the most emaciated and ill patients, but did not depend on the degree of temperature elevation at the time of the test. It is interesting that the coexistence of pulmonary tuberculosis and hypertension is said to be uncommon.[9] The reason for the small response to paredrine in this group of patients is not evident. The absence of cardiac slowing was interpreted as a result of the failure of hypertension to develop.

Fever did not influence the pressor activity of paredrine in any of the experiments designed to test its effect, and several of the subjects

with acute infections and high fever showed a good response to paredrine. The decrease in response to paredrine during fever in several of the subjects was probably due to the vasodilatation usually associated with febrile states. Chasis, et al.,[10] observed that the injection of pyrogenic materials produces a fall in the blood pressure of hypertensive subjects, and Goldblatt, et al.,[11] believe that a favorable response to depressor substances in hypertension may be related to the appearance of fever.

Abnormal rhythms after the intravenous injection of paredrine in man were not noted by Loman, et al.,[2] or by Iglauer and Altschule;[4] neither group made electrocardiographic studies. An increase in height of T waves without change in rhythm has been noted previously in normal subjects after the oral administration of paredrine.[12]

Abbott and Henry[1] reported "extra-systoles and coupling of the beats" after the oral and intramuscular administration of paredrine, but did not discuss electrocardiographic observations. American observers have likewise failed to comment on arrhythmia after the administration of paredrinol. European authors, however, have reported changes in rhythm after the injection of paredrinol (veritol); these included nodal rhythm, extrasystoles, parasystole, interference dissociation, and complete A-V dissociation.[13, 14]

Keys and Violante, in a recent article,[15] report complete A-V dissociation and changes in P waves in human subjects after the injection of neosynephrin, a substance whose mode of action appears to be similar to that of paredrine. The same authors reproduce an electrocardiogram showing inversion of the P wave and shortening of the P-R interval after the injection of 10 mg. of synephrin tartrate subcutaneously.[16] These changes resemble those interpreted in the present study as indicating A-V nodal rhythm. Adrenalin has also been found to produce ventricular premature contractions and changes in the P wave and P-R interval in man.[17]

The production of arrhythmia by paredrine may be related to the occurrence of hypertension rather than to a direct effect on the heart, for it seems to occur only when hypertension is produced. Vagal depressor reflexes, mediated through the carotid sinus or aortic depressor mechanisms, probably cause the cardiac slowing which occurs during hypertension produced by paredrine, for the decrease in rate may be prevented or abolished by atropine[4] (Case 15). The electrocardiographic changes which are observed in most of the patients, i.e., nodal rhythm, wandering pacemaker, and slow rate, are thought to be due to vagal stimulation.[18] Arrhythmias which occur after the intravenous administration of paredrine have been found to disappear within two to three minutes after the injection of 0.65 mg. of atropine intravenously.[12] The occurrence of transient arrhythmias after the intravenous injection of paredrine need not be considered a contraindication

to the therapeutic use of this compound, for the rhythms encountered do not interfere markedly with cardiac function, nor are they of the type which might be considered as precursors either of ventricular fibrillation or cardiac arrest.

SUMMARY AND CONCLUSION

1. The effect of the intravenous injection of paredrine on the cardiovascular system has been studied in twenty-eight subjects; these included patients with infections, patients with fever produced for therapeutic purposes, and a control group.

2. Intravenous doses of 6 to 10 mg. did not cause severe discomfort or untoward reaction.

3. In nine patients with infections other than tuberculosis, paredrine produced a marked pressor response. Three of the eleven tuberculous patients showed a much smaller pressor response, and five other patients of this group had only a moderate or shortened pressor response to paredrine.

4. Four patients were studied before and during fever produced by the injection of typhoid vaccine; three showed a smaller response during fever. In one patient with malaria the pressor response was moderately diminished during a febrile period.

5. Changes in cardiac rhythm appeared frequently. The electrocardiogram showed wandering of the pacemaker in three subjects. Ectopic rhythms, probably originating in the auriculoventricular node, were observed in seven subjects. The arrhythmias were attributed to reflex vagal stimulation.

6. The cause of the relatively slight pressor response to paredrine in some of the patients of the present series is not apparent.

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Clinical Reports

THE ELECTROCARDIOGRAPHIC MANIFESTATIONS OF EARLY ACUTE COR PULMONALE

CHARLES H. SCHEIFLEY,* M.D., AND THOMAS J. DRY,† M.B.
ROCHESTER, MINN.

THE electrocardiographic changes associated with pulmonary embolism represent, in the main, the effects of suddenly produced, acute, right ventricular strain. These changes conform to well-established trends of electrocardiographic behavior. Thus, a prominent S wave in Lead I, an R wave in Lead III (expressing, in reality, right axis deviation), an inverted T wave and a deep Q wave in Lead III, a small or isoelectric T wave in Lead II (rarely inverted), arising from an S-T segment that has an isoelectric or depressed S-T junction, and inversion of the T waves in precordial leads taken at the C_2 position and at times in precordial leads obtained from position IV, have become well-recognized criteria of pulmonary embolism. When the T waves obtained in the C_2 position are negative, and, at the same time, the T waves obtained at position IV are positive, the evidence is specific for acute right ventricular strain, usually due to pulmonary embolism. It should be emphasized, however, that the electrocardiographic diagnosis of pulmonary embolism should depend on the pattern of changes observed in all the leads, rather than isolated electrocardiographic changes.

A noteworthy feature of the electrocardiographic changes associated with pulmonary embolism is their temporary nature. This would be accounted for most satisfactorily if it could be proved that an embolus in a pulmonary artery leads to transitory vasospastic phenomena throughout the pulmonary arterial tree, and there is some reason to believe that this is what occurs.[1, 2] It is to be expected, therefore, that the most marked electrocardiographic changes will be present shortly after the occurrence of embolism, and that a gradual trend toward normal will follow if the patient survives the attack.

One of the early changes which has not been stressed in all reports (although reproductions of some electrocardiograms[3, 4] show it) is a marked widening and slurring of the S wave in Lead I or Leads I and II which closely resemble the type of bundle branch block that is reputedly due to a conduction disturbance in the right bundle branch.

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*Fellow in Medicine, Mayo Foundation.
†Section on Cardiology, Mayo Clinic.

In one of Pick's cases the curve was of this type.[5] In this case an electrocardiogram was made immediately after the occurrence of pulmonary embolism.

Furthermore, Durant, Ginsberg, and Roesler[6] reported three cases of pulmonary embolism in which electrocardiograms made soon after the onset of symptoms showed delayed intraventricular conduction of the right bundle branch type, with a broad, shallow S wave in Leads I and II, and marked depression of the S-T segments in these leads. Within five to twelve hours after the onset of the pulmonary embolism, the bundle branch block had disappeared, leaving depressed S-T segments and a "staircase" type of ascent to the T wave.

We wish to report a case which illustrates the early electrocardiographic manifestations of pulmonary embolism unusually well. In this case we were fortunate enough to obtain a record immediately after an attack of pulmonary embolism which proved fatal shortly afterward.

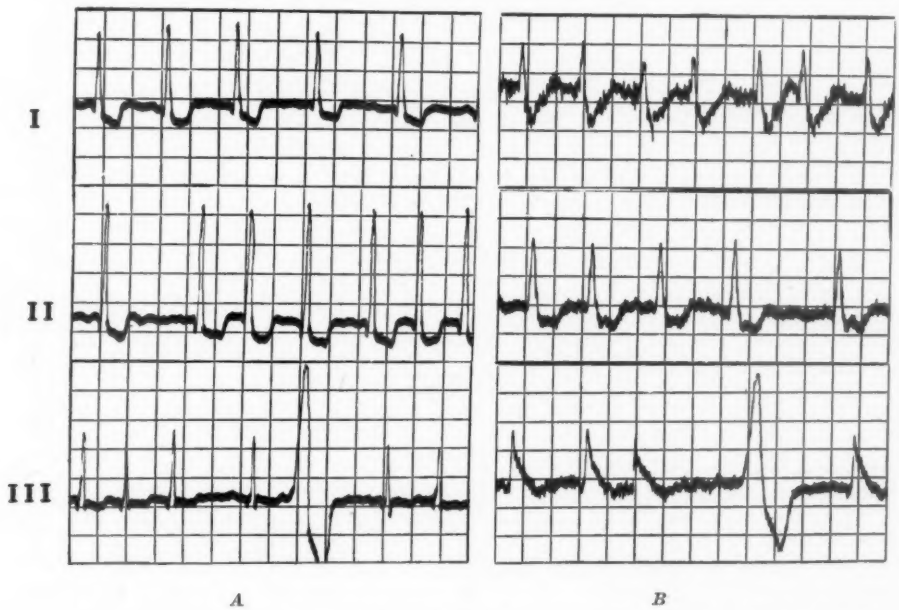

Fig. 1.—*A*, Electrocardiogram made on admission of patient; note the depressed S-T segments in Leads I and II, with inverted T waves in these leads (effect of digitalis); *B*, record made five minutes after the occurrence of pulmonary embolism. Bundle branch block, with a wide S wave in Leads I and II and S-T segment depression in these leads.

REPORT OF CASE

The patient was an obese woman, 64 years old. Two months before admission she had been awakened by a fluttering sensation around her heart. In the light of subsequent observations this probably indicated the onset of auricular fibrillation. She also had begun to notice a considerable degree of weakness. Digitalis had been prescribed by her family physician, but the response was not very satisfactory.

On admission, she had symptoms of mild congestive heart failure. The blood pressure was about 200/110. There was definite cardiac enlargement. The auricles

were fibrillating and the ventricular rate was 164 beats per minute. Hyperthyroidism was suspected because of the rapid ventricular rate, muscular weakness, moderate intolerance of heat, and a small adenoma of the left lobe of the thyroid gland. She had, in addition, an afternoon temperature of about 100° F. (37.7° C.). Under these circumstances accurate measurement of the basal metabolic rate was impossible, and definite exclusion of hyperthyroidism was therefore difficult.

We were unable to ascertain from the patient's history how much digitalis she had taken prior to admission, but the electrocardiogram revealed marked changes in the S-T segment of the type which is common after digitalization of a patient with a condition producing strain of the left ventricle (Fig. 1*A*).

The patient was hospitalized for further observation and treatment. On the fourth day, pain developed, pleuritic in character, in the left side of the thorax. This was followed three days later by the coughing up of bloody sputum, so that it was quite apparent that she had pulmonary embolism. Her condition was improving satisfactorily until two weeks later, when she suddenly became weak and complained of pressure over her chest. She was gasping for breath and showed signs of shock. An electrocardiogram was made immediately. She died about ten minutes later.

This electrocardiogram (Fig. 1*B*) showed marked changes as compared with the former one. The changes consisted essentially of a widening of the QRS complexes. It is to be noted that this was caused by a markedly slurred and widened S wave. At necropsy the heart was found to be enlarged, and weighed 580 grams. A moderate degree of sclerosis existed throughout the coronary tree, although it was more marked in the descending branch of the left coronary artery. There was no cardiac infarction. Fresh emboli were present in both pulmonary arteries, and there were old infarcts in the left lung, with overlying pleuritis. There was extensive thrombus formation in the femoral and iliac veins. The nodule in the left lobe of the thyroid gland was found, on microscopic examination, to be merely a fetal adenoma.

COMMENT

If it can be said that there is a type of person who might be expected to have pulmonary embolism, this patient conformed to that type. She was obese, and a factor favoring venous stasis and the formation of thrombi, namely, congestive heart failure, was present. The frequency with which one attack of pulmonary embolism is likely to be followed by another is also well illustrated in this case.

The extensive thrombus formation in the femoral and iliac veins is worthy of note. Very frequently it is assumed that the source of pulmonary emboli among patients whose auricles are fibrillating is the right auricle. Although this must be true in some cases, it is more than likely that in most instances the emboli originate in the peripheral venous system.

The electrocardiogram which was made within five minutes of the occurrence of the pulmonary embolism showed an abnormality of the QRS complex of the type which has been observed after experimental pulmonary embolism[6] and also after experimental section of the right bundle branch.[7] It is possible that digitalis may have contributed to these changes.

This record further resembles the type of ventricular conduction disturbance which has been designated as the "wide S-wave pattern," and

is believed to represent right bundle branch block.[8] This is most commonly associated with coronary sclerosis, and is a permanent rather than a transitory state.

Considerable evidence[9-11] is available to show that among patients who have a wide S-wave pattern there is an asynchronism between the beats of the two ventricles, and the left contracts before the right. In the presence of pulmonary embolism the right ventricle is suddenly subjected to a tremendously increased load (acute right ventricular strain), apparently caused in part by reflex spasm of the entire pulmonary arterial bed.[2, 12, 13] Among patients who survive, the right ventricle rapidly dilates and is at first unable to cope efficiently with this resistance. Asynchronism of the two ventricles can readily be accounted for by such a disturbance. It is at this stage that the electrocardiographic picture of delayed intraventricular conduction, resembling one type of right bundle branch block, is seen.

The possibility that a reflex constriction occurs in the coronary arterial tree also has been postulated to explain the electrocardiographic characteristics of pulmonary embolism. This concept has received considerable support from the results of experiments which have revealed the presence of sensitive vasoreceptors in and around the pleura,[14] bronchi,[15] and pulmonary arteries,[16, 17] the stimulation of which produced widespread reflex changes, some of which suggested coronary constriction. De Takats and his co-workers[18] obtained electrocardiograms from dogs after the production of experimental pulmonary embolism, and they were of the type which indicates interference with the coronary circulation. Clinical evidence, aside from electrocardiographic phenomena, that pulmonary embolism may produce coronary artery spasm is derived mainly from reports of cases in which only small portions of the lung were infarcted, but in which the outcome nevertheless was fatal.

Friedberg and Horn[19] reported that twelve instances of myocardial infarction *without* coronary occlusion were found in cases of pulmonary embolism in which the outcome was fatal. This would constitute certain evidence in favor of the theory of reflex production of coronary artery spasm, were it not for the fact that four of their patients had angina, four had hypertension, and three had symptoms of congestive heart failure, in all of which cardiac infarction may occur without demonstrable coronary artery occlusion.

SUMMARY

A case is presented which demonstrates the early electrocardiographic manifestations of acute cor pulmonale. The characteristic abnormality at this stage is a wide, slurred S wave, especially in Lead I. This widening of the S wave tends to recede after a few hours, and the electrocardiographic pattern then becomes the same as that previously described

as typical of pulmonary embolism. The physiologic basis for these changes is discussed.

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CORONARY THROMBOSIS AND MYOCARDIAL INFARCTION IN YOUTH

Report of a Case, With Autopsy, in a 19-Year-Old Male

L. Zacks, Captain, R.C.A.M.C.
Montreal, Can.

SINCE the classical clinical descriptions of coronary thrombosis by Obratzow and Strascheko,[1] in 1910, and by Herrick,[2] in 1912, the clinical diagnosis of this disease has been made with increasing frequency and accuracy. Although coronary thrombosis is ordinarily regarded as a disease of late middle life (45 to 60 years), recent reports have shown that it occurs occasionally in persons under 20 years of age.

A review of the literature disclosed eight cases[3a-g*] of coronary thrombosis between the ages of 10 and 20 years. In six of these the diagnosis was confirmed by autopsy, and in two cases[3b] the diagnosis rested upon clinical evidence alone. Review of the literature also revealed five cases[4a-e] of medial coronary sclerosis in infants from birth to 27 months, in which evidence of myocardial damage (presumably infarction) was present.

It is of interest that, during the past decade, the literature contains an ever increasing number of references to the incidence of coronary thrombosis among persons between 25 and 40 years of age.[5a-b] Whether this apparent increase in incidence is real or dependent upon our changing mode of life, or whether it is due to improved clinical acumen and lack of hesitancy upon the part of the clinician to make the diagnosis in youth is beyond the scope of the present report.

Although the case to be reported offered no problem in clinical diagnosis (because of the classical history and characteristic manifestations), yet because of the patient's age and the opportunity to corroborate the diagnosis post mortem, this case is added to the group of eight patients from 10 to 20 years of age who have been reported.

CASE REPORT

History.—D. B., a 19-year-old Jewish boy, was admitted to the Jewish General Hospital for the first time on April 18, 1941, to the medical service of Dr. H. N. Segall, with a history of precordial pain upon exertion, of one year's duration. This pain was accompanied by a feeling of oppression, and radiated to the epigastrium, left shoulder, and down the left arm, and was relieved by one to two hours' rest. These attacks would come on at work or upon hurried walking. Upon more detailed questioning he admitted that these symptoms first commenced in the

From the Departments of Pathology and Medicine, Jewish General Hospital, Montreal.

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*The cases of Huchard, mentioned in Allbutt and Rolleston's *System of Medicine*, Vol. 6, p. 172, 1909, are not included because of inability to obtain the original reference.

autumn of 1937. At that time, however, they were infrequent, and of such a mild, transitory nature that he dismissed them as being inconsequential. In the preceding year the pains had increased both in frequency and severity, and, upon one occasion, he sought the advice of his family physician, who suggested a thorough checkup. The patient disregarded this advice.

On the morning of admission, while at work, he experienced a sensation of dizziness and decided to go home. As he mounted the streetcar, he was suddenly seized with severe precordial oppressive pain, which radiated to the left shoulder and arm and was not relieved by rest as it had been in the past. He left the streetcar and could not continue homeward. He sat down on a doorstep, called a cab, and presented himself at the hospital for admission.

The patient worked as a shipper, and did moderately heavy manual labor. He had smoked about twenty-five cigarettes a day until three months before, at which time he cut his consumption to five or ten cigarettes a day. His past history revealed only occasional, postprandial, right upper quadrant distress after the ingestion of fatty or fried foods, occasional headaches and dizziness, and infrequent pains in the knee joints.

His mother had hypertension, with a blood pressure of 170/100, and electrocardiographic evidence of myocardial disease. There was no other family history of cardiovascular disease.

Physical Examination.—The patient was a healthy looking, well-developed, and well-nourished white boy who was in some distress as he lay in the dorsal recumbent position.

The heart was not enlarged to percussion. There was a loud systolic murmur at the apex. The pulmonic second sound was louder than the aortic second sound. The blood pressure was 142/86. There was a questionable respiratory lag of the right side of the chest, with many fine, moist râles over the lower half of the right side and a few at the left base. The rest of the examination was negative.

Laboratory and Special Clinical Examination.—Urinalysis, negative. Erythrocyte count, 5,150,000; hemoglobin, 102 per cent; leucocyte count, 14,000; differential count: polymorphonuclear leucocytes, 78 per cent, lymphocytes, 17 per cent, monocytes, 3 per cent, eosinophiles, 2 per cent.

The electrocardiogram was remarkably abnormal; it showed slurred QRS complexes in all leads, and depressed S-T segments in Leads I, II, and III, suggesting recent myocardial infarction.

A roentgenogram of the chest showed pulmonary congestion.

Progress.—His course in the hospital was brief. Morphine afforded slight relief from pain, and the patient slept comfortably from midnight to 5:30 A.M., when his condition became very poor. He had an ashen color, was deeply cyanosed, sweated profusely, and had a thready pulse of 120 per minute. His breathing was labored, and he coughed up pink-stained, foamy sputum. The chest was full of râles, the heart sounds were distant, and his blood pressure had fallen to 108/80. Because of this fall in blood pressure, no phlebotomy was performed. He was placed in an oxygen tent and given pantopon. He continued to grow worse, and died one hour later, approximately twenty hours after admission.

The clinical diagnoses were coronary occlusion, myocardial infarction, and acute pulmonary edema.

Autopsy (performed by Dr. M. A. Simon, nine hours after death).—The body was that of a well-developed and well-nourished white man. There was marked cyanosis of the mucous membranes and nail beds, and frothy, bloody fluid exuded from the mouth.

The heart weighed 390 grams, but was of the usual shape. The epicardium was everywhere thin, smooth, and transparent. Over the anterior and lateral aspects

of the apical portion of the left ventricle the small veins were prominent and injected. The myocardium at this point was somewhat more flabby in consistency than elsewhere. The auriculoventricular sulcus was not obliterated. The coronary arteries were straight and pliable to palpation. The left circumflex branch ended on the obtuse margin of the left ventricle, but the right coronary artery crossed the midline posteriorly to supply the posterior aspect of the left ventricle. Upon section, all chambers were of the usual size and shape. The endocardium throughout was smooth and glistening, and no mural thrombi were seen. All of the valves showed thin, delicate, and translucent leaflets in which no anomalies or evidence of gross pathologic change was present.

Section through the lateral aspect of the left ventricle showed a somewhat granular, mottled yellow and red myocardium that was flabby in consistency. On anterior section through the left ventricle, parallel to the interventricular septum, the myocardium showed the same mottled appearance, but, in addition, a few gray, fibrous streaks could be seen in the muscle of the interventricular septum.

The left coronary orifice was of the usual size and shape, but, upon looking into it from the aorta, the lumen was found to be filled with a loosely adherent, grayish-red blood clot. This recent thrombus completely occluded the common left coronary trunk, and extended into the left circumflex branch for a distance of 5 mm. Beyond the point of occlusion in the left circumflex branch the coronary wall was thin and pliable and the intimal surface was smooth and glistening.

Transverse sections through the left descending ramus showed that the lumen was completely occluded for a distance of 15 mm. beyond its origin by a firmly adherent, mottled red and grey thrombus that differed from the thrombus occluding the common trunk and left circumflex branch. Beyond this region, in the left descending ramus, the lumen was empty. The walls were thin and pliable and the intimal surface was smooth and glistening.

The right coronary orifice was of the usual size and shape and was not occluded. Section revealed thin, pliable walls, and an occasional, tiny, yellow intimal plaque which did appear to reduce the caliber of the lumen. The right coronary artery coursed beyond the midline posteriorly, and supplied the posterior aspect of the left ventricle.

The aorta showed a few yellow, atheromatous streaks near the orifices of the vertebral arteries. The lungs were the seat of edema and passive hyperemia. All other viscera and the brain showed only passive hyperemia.

Microscopic Examination.—A section taken through the left descending ramus, close to the point of origin, showed complete obliteration of the lumen by a well-organized and canalized thrombus (Fig. 1). The thrombus was composed of granulation tissue, and contained many lymphocytes, occasional plasma cells, and moderate numbers of polymorphonuclear leucocytes. The thrombus contained many endothelial-lined spaces containing erythrocytes, and, within two of these vessels, recent thrombi, showing beginning organization, were present.

The intima of the coronary artery was irregularly thickened, and, in one location, was elevated and composed of lamellated, relatively acellular, fibrous connective tissue containing a few acicular slits. The media was thin and intact throughout, and, in the thickened, fibrous adventitia, a few thick-walled arterioles and capillaries with perivascular collars of lymphocytes were encountered. A section stained by the Weigert method revealed splitting and fragmentation of the internal elastic lamella. The external elastic lamella was intact throughout, and several fine elastic fibers were seen in the media.

A section through the left circumflex artery immediately beyond its point of origin (Fig. 2) showed that the lumen was completely occluded by a recent lamellated thrombus composed of layers of erythrocytes, fibrin, and leucocytes. In one area

this thrombus showed beginning organization. The left circumflex showed irregular intimal thickening, and, at one point, a large, spherical plaque narrowed the lumen in an eccentric fashion. In the lowermost portions of this plaque several focal collections of histiocytes and round cells were seen. The internal elastic lamella showed only slight focal fragmentation. The media was not remarkable.

A section of the interventricular septum taken at right angles to the longitudinal axis of the left descending coronary artery revealed two branches of the descending ramus lying in fat. These were the seat of completely organized and canalized thrombi. In the interventricular septum there were large, irregular, well-vascularized areas of fibrous tissue, which separated and replaced large masses of myocardial fibers. In addition to this change, the deeper portions of the myocardium showed loss of staining quality, with loss and pyknosis of nuclei and a sparse but diffuse infiltration of polymorphonuclear leucocytes.

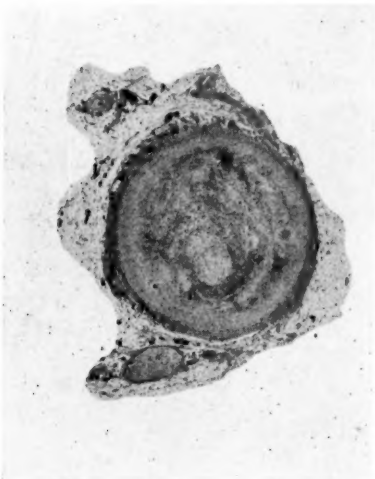

Fig. 1.

Fig. 2.

Fig. 1.—Section of left descending coronary ramus showing subintimal fibrosis and thrombosis, with canalization and subsequent thrombosis of canalized vessels.

Fig. 2.—Section of left circumflex coronary branch just beyond its origin. Note the marked eccentric subintimal fibrosis of wall and reduction in lumen. The lumen is filled with a recent and lamellated thrombus which was continuous with thrombus plugging the canalized vessels of a remote thrombus in the left descending ramus.

A section through the posterior aspect of the left ventricle revealed marked loss of staining quality of muscle fibers, granularity of cytoplasm, destruction and pyknosis of nuclei, and diffuse interstitial infiltration by large numbers of polymorphonuclear leucocytes. A small amount of interstitial hemorrhage was present.

Sections of the lungs showed pulmonary edema and passive hyperemia. All other sections showed only passive hyperemia.

Anatomic Diagnosis.—Coronary arteriosclerosis; remote coronary thrombosis of left descending ramus, with organization, canalization, and recent, superimposed, thrombosis; recent thrombosis of left circumflex branch; remote and recent infarction of interventricular septum; recent infarction of left ventricle; pulmonary edema; hydrothorax, bilateral; chronic passive hyperemia of viscera.

DISCUSSION

The type of coronary arteriosclerosis in this case differed slightly from that of older persons, in that less atheroma and no calcification were

present. The subintimal lesion was fibrous in nature, but the few acicular slits indicated that conversion of cholesterol esters to crystals had occurred. According to Leary,[6] the characteristic lesion of coronary sclerosis in young persons is fibrosis associated with lipoid cells which do not accumulate in large aggregations because of the growth of fibrous tissue. He is of the opinion that the cause of death in the young is thrombosis secondary to subendothelial necrosis which extends to the endothelium. No distinct subendothelial necrosis could be demonstrated in the present case.

Of the cases of coronary thrombosis between the ages of 5 and 20 years previously reported, adequate microscopic studies are available in only three. Thus, in the cases of Sprague and Orgain[3a] and of Benda,[3e] at the ages of 15 and 12 years, respectively, characteristic atherosclerotic changes were present, whereas, in the case reported by Jamieson and Hauser,[3f] that of an 18-year-old boy, the larger coronary branches showed a purely degenerative arteriosclerosis, with slight calcification, and the smaller branches showed proliferating endarteritis.

In infants between the time of birth and the age of 27 months the coronary artery changes are quite different from the usual sclerotic changes in adults. They consist of medial calcification, with or without intimal thickening, and resemble the changes which occur in experimental animals after overdosage with parathyroid extract[7] or vitamin D.[8] No proof is presented in any of the reported cases of coronary sclerosis in infants that overdoses of vitamin D were given, and the cause of these medial changes remains controversial.

The patient in the present case suffered severe anginal attacks for at least one year before death. This is understandable because of the marked reduction in the lumen of, and hence in the blood flow through, the left descending ramus. The thrombus, however, was well canalized, and must have permitted sufficient flow of blood to nourish the interventricular septum until the last attack. It was not until the final thrombus occluded the left circumflex branch, as well as a few of the canalized vessels in the thrombus of the descending ramus, that death occurred. Sections through the interventricular septum showed patchy areas of fibrosis and bland necrosis of the myocardium, but, in addition, a few areas of leucocytic infiltration were seen. Sections from the posterior aspect of the left ventricle showed much more extensive leucocytic infiltration, accompanied by necrosis of the myocardium. These observations suggest that the initial thrombosis of the left descending ramus did not completely occlude this artery, but gradually grew by accretion and became organized and canalized, and that it was not until the final thrombus occluded not only these canalized vessels, but the circumflex branch as well, that death ensued.

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   (c) Meakins, J. C., and Eakin, W. W.: Coronary Thrombosis: A Clinical and Pathological Study, Canad. M. A. J. **26**: 18, 1932.
   (d) Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction, Am. J. M. Sc. **183**: 215, 1932.
   (e) Benda, C.: A Case of Severe Infantile Coronary Thrombosis as Cause of Death, Virchows Arch. f. path. u. path. Anat. **254**: 600, 1925.
   (f) Jamieson, S. C., and Hauser, G. H.: Angina Pectoris in a Youth of 18, J. A. M. A. **85**: 1398, 1925.
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   (b) Brown, C. E., and Richter, I. M.: Medial Coronary Sclerosis in Infancy, Arch. Path. **31**: 449, 1941.
   (c) Ramsay, R. E., and Crumrine, R. M.: Coronary Thrombosis in an Infant Aged 4 Months, Am. J. Dis. Child. **42**: 107, 1931.
   (d) Hughes, F. W. T., and Perry, C. B.: Senile Arterial Changes in a Child Aged 7 Months, Bristol Med.-Chir. J. **46**: 219, 1929.
   (e) McMichael, J.: Extensive Visceral Endarteritis Obliterans in a Young Child, Arch. Dis. Childhood **4**: 165, 1929.
5. (a) Master, A. M., Dack, S., and Jaffe, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, Arch. Int. Med. **64**: 767, 1939.
   (b) Glendy, R. E., Levine, S. A., and White, P. D.: Coronary Disease in Youth, J. A. M. A. **109**: 1775, 1937.
6. Leary, T.: Experimental Atherosclerosis in Rabbit Compared With Human (Coronary) Atherosclerosis, Arch. Path. **17**: 453, 1934.
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Abstracts and Reviews

Selected Abstracts

Wégria, R., Rojas, A. G., and Wiggers, C. J.: A Study of Spontaneous Fulminant Shock in a Heart-Lung-Dog Preparation. Am. J. Physiol. **138**: 212, 1943.

The relative importance of (a) decrease in venous pressure and secondary reduction of cardiac output, (b) primary myocardial impairment, and (c) changes in total peripheral resistance (TPR) in shock was studied by means of a heart-lung-dog preparation, which is described. Venous flow and cardiac output were under control, and TPR could be calculated. In such a preparation, a fulminant type of shock develops spontaneously which may resemble clinical types characterized by speedy circulatory failure and death.

In twenty-four such experiments it was shown (a) that shock can develop without progressive reduction or even with a rise of venous pressures or cardiac output, and (b) that it cannot be prevented or cured by increased venous inflow and cardiac output.

The fundamental factor responsible for this type of irreversible circulatory failure was a steady and pronounced decrease in total peripheral resistance, which enabled the animal to store, over and above its own blood volume, quantities of blood equal to 25 per cent of its body weight, or four times its own blood volume. Autopsies revealed no storage depots other than the mucosa of the upper intestines, which was always edematous, intensely congested, and often hemorrhagic. The integration of these observations with apparently contrary findings regarding the state of the peripheral circulation, and their application to fulminant types of shock in man are discussed.

Following any prolonged period of hypotension during the development of shock, the cardiac output at equivalent venous pressures also decreased, indicating that depression of the myocardium occurred. In the form of shock studied, this did not prove to be an initiating factor nor was it necessary to produce an irreversible state. But, after the peripheral changes of shock had been well established, it played an important role in the rapid downward trend of blood pressure and was the ultimate cause of death.

Five dogs, primed with liberal doses of cortical adrenal extracts, and receiving these extracts during the experiments, revealed no indications that the course of dynamic events or the pathologic changes in the intestinal mucosa were influenced. It must be recognized, however, that the authors' preparations perhaps offered too severe a test.

AUTHORS.

Simister, T. H., and Conklin, R. E.: The Role of Pressoreceptors in the Regulation of Blood Pressure in the Rabbit. Am. J. Physiol. **138**: 391, 1943.

Brief tipping experiments have been done on thirty-two rabbits, with progressive elimination of sources of afferent impulses causing reflex circulatory compensation. It has been shown that the rabbit is still able to compensate to some extent for the effect of gravity when it is deprived of vagi, aortic nerves, carotid sinuses and splanchnic nerves. Some other reflexogenic sources, responsible for the compensation, must exist.

AUTHORS.

Ponder, E., and Hyman, C.: The Cytologic Effect of Saponin on the Walls of Vessels. Am. J. Physiol. **138**: 432, 1943.

When frog muscle is perfused with saponin or bile salts in frog Ringer, the permeability of the vessel walls is increased, and this results in an increased rate of edema formation. If the muscle is perfused with a solution of hemoglobin to which saponin or bile salts have been added, the hemoglobin, which in the absence of the lysins, remains in the vessels, escapes through the vessel walls and appears in the extravascular spaces. While these effects are being produced, the lysins disappear, in part, from the perfusion fluid, being taken up by the vessel walls and other tissue cells. Quantitative determinations of the rate of uptake of the lysins, and of their effects on permeability, show that the kinetics of the cytolytic process are similar to the kinetics of hemolytic processes. The quantities of saponin involved in producing these changes in permeability are such as would cover the walls of the vascular system of the muscle with a layer of lysin less than ten molecules thick.

AUTHORS.

Bernstein, S. S., and Ginzburg, L.: Status Anginosus Due to Profound Anemia. J. Mt. Sinai Hosp. **9**: 142, 1942.

Angina pectoris of increasing severity appeared in a 62-year-old man suffering with profound anemia due to two independent gastrointestinal neoplasms. The cardiac pain was promptly relieved following transfusions, and never recurred after two operative procedures, even with the resumption of full activity.

KERSHBAUM.

Dill, D. B.: Physiology of Flying. J. Lab. & Clin. Med. **28**: 585, 1943.

Graybiel, A.: Some Problems in Aviation Medicine. J. Lab. & Clin. Med. **28**: 590, 1943.

Dill, D. B.: Physiology of Fatigue: Factors and Criteria of Endurance. J. Lab. & Clin. Med. **28**: 596, 1943.

These three lectures were part of a series given at the Metropolitan State Hospital, Waltham, Mass. The authors discuss the general problems involved in aviation medicine, particularly the response of the heart and circulation to abnormal conditions of flying. Much of the material is the application of studies on fatigue made by the authors. The lectures are of value to the cardiologists who may find themselves engaged in aviation war medicine.

MCCULLOCH.

Lewis, T.: Swelling of the Human Limbs in Response to Immersion in Cold Water. Clin. Sc. **4**: 349, 1942.

When an extremity is cooled, as by immersion in cold water (5° C.), it swells. This increase of volume occurs in both skin and subcutaneous tissue, and within three hours may amount to as much as 15 per cent of the original volume.

The swelling is due mainly to an edema of the tissues, judged to be inflammatory from its relatively rapid outpouring and from its relatively high protein content. The contribution in the form of imbibed water is very slight.

From this and correlated evidence, it seems that cold directly injures the skin and subcutaneous tissues. This effect begins at about 15° to 18° C. and increases as the scale of temperature is descended.

The production of edema as a result of long-continued immersion of the limbs in cold water should be taken into account, as should protein loss, in estimating the effects of exposure to cold upon the whole circulation.

AUTHOR.

Wolferth, C. C., Livezey, M. M., and Wood, F. C.: Distribution of the Patterns of Ventricular Potential Which Determine the Forms and Significance of Electrocardiograms. Am. J. M. Sc. **205**: 469, 1943.

Much of the confusion which now exists in clinical electrocardiography could be eliminated if, in all leads, one of the paired electrodes were attached to an area of relatively slight potential variation, such as the right scapular region. Under such circumstances, an electrocardiogram may be obtained which presents a relatively undistorted record of the potential variations of the exploring electrode. From data now available, it is possible to say that the exploring electrode should be placed on a number of chest positions such as C_1 to C_6 inclusive, if one wishes to acquaint himself with the chief features of the various patterns which may be formed on the surface of the chest, including the two widely distributed to the upper parts of the trunk and arms. In order to obtain information regarding the pattern widely distributed below the diaphragm, it is necessary to place the exploring electrode on some position at least a few inches below the parietal attachments of the diaphragm. The best position or set of positions for this purpose has not as yet been determined.

AUTHORS.

Nylin, G., and Grewin, K. E.: Three Chest Leads and Their Value in Association With the Leads From the Extremities, and Several Other Chest Leads. Cardiologia **6**: 169, 1942.

Some of the formerly introduced chest leads, and three, proposed by Nylin, called the longitudinal, the transverse, and the sagittal lead, are described. The importance of an exact localization of the lead off points by means of radioscopy is argued. About 350 heart cases have been examined with the above mentioned leads and part of them with the Nehb, Jervell, and CF_4 leads. The transverse lead is of little value; the longitudinal and the sagittal ones, however, possibly are valuable. The Nehb leads are to be further investigated, since they seem to be valuable especially the dorsal one, for the diagnosis of posterior infarction.

AUTHORS.

Rosenbaum, F. F., Johnston, F. D., and Keller, A. P.: Paroxysmal Ventricular Tachycardia in Childhood. Am. J. Dis. Child. **64**: 1030, 1942.

A review of the literature has disclosed seven cases of paroxysmal ventricular tachycardia in childhood, which satisfy the criteria necessary for this diagnosis. Two additional cases, recently observed in this clinic, are reported.

The first case was that of a child with congenital heart disease who had had ventricular tachycardia for two weeks. The paroxysm ceased only after a large amount of quinidine was given. For a few days thereafter, the patient exhibited unusual forms of independent auricular and ventricular rhythms, together with alternations in the form of the ventricular complexes.

The second case was that of a boy with no evidence of structural heart disease, who had frequent, symptomless paroxysms of ventricular tachycardia of short duration. The arrhythmia disappeared on exertion.

Measures usually employed in the treatment of supraventricular tachycardia are without effect in ventricular tachycardia, and it is therefore essential to differentiate

these two types of tachycardia whenever a case of paroxysmal rapid heart action of significant duration is encountered. Careful clinical and electrocardiographic studies should be made to determine whether the tachycardia is supraventricular or ventricular in origin, and if it is the latter, quinidine sulfate should be given in adequate dosage to convert the rhythm to normal.

AUTHORS.

Strauss, S., and Langendorf, R.: Bilateral Partial Bundle Branch Block. Am. J. M. Sc. **205**: 233, 1943.

A case is reported of sinus rhythm with intraventricular block showing variations of the ventricular complexes between the common and uncommon types. This change is associated with the occurrence of advanced partial A-V block. The alternations are explained by assuming partial block in the two main bundle branch systems, with a shorter relative refractory phase of the bundle branch which has the longer absolute refractory phase.

AUTHORS.

Rhodes, P. H., and Durbin, E.: Coarctation of the Aorta in Childhood: Review of the Literature and Report of Three Cases. Am. J. Dis. Child. **64**: 1073, 1942.

A review of the literature on coarctation of the aorta revealed forty-seven cases in which adult type had been diagnosed during life in children under 15 years of age. It is important to make the diagnosis of coarctation as early in childhood as possible, since the life of the patient may be prolonged by prohibiting strenuous sports and occupations.

When coarctation of the aorta is pronounced enough to give clinical signs, its diagnosis is not difficult if the condition is kept in mind. It should be suspected when forceful pulsations in the neck, and hypertension, particularly with a wide pulse pressure, are observed in the child. The presence of a much lower blood pressure in the lower extremities and of retardation and diminution of pulsation in the femoral arteries confirms the diagnosis. The finding of a collateral circulation, and the roentgenologic signs are valuable aids.

If routine determinations of blood pressure in children are made only on one arm, the right arm should be used, in order to avoid overlooking the occasional cases of coarctation in which the pressure is low in the left arm. Such a case is reported, together with interesting electrocardiographic observations.

AUTHORS.

Leys, D.: Congenital Heart Block With Dextrocardia. Brit. Heart J. **5**: 8, 1943.

A patient with congenital heart block, dextrocardia, and probable septal defect is reported. She also developed extensive pulmonary tuberculosis, but showed a good tendency to recovery, and attained the age of 23 years with good functional capacity equal to office work. Her ventricular rate was about 50, but rose to 80 during fever. It was not influenced by exercise or adrenalin.

AUTHOR.

Heilig, R.: The Pathological Heart Conditions in Hookworm Disease and Their Causes. Indian M. Gaz. **77**: 257, 1942.

The observations on sixty-five cases of uncomplicated, afebrile, severe hookworm disease, reported and discussed above, make it certain that the pathologic heart signs

which are typical for this condition are due to a diffuse myocardial damage which leads to a considerable dilatation of the left and the right heart; the murmurs are not only hemic but also, most probably, consequences of a functional, supravalvular pulmonary stenosis and a relative mitral insufficiency, caused by the dilatation. In 90 per cent of these cases all the signs of myocardial degeneration and dilatation vanished quickly and almost completely in parallelism with the improvement of the erythrocyte count and hemoglobin level, in spite of the untreated and persisting hookworm infestation. Six cases showed no change of the pathologic heart condition before deworming, though the hemoglobin level rose from values of 10 to 15 per cent Sahli on admission, to 40 to 60 per cent before anthelmintic treatment was started; in these cases the heart dilatation and myocardial lesion improved quickly after complete destruction of the hookworms. These facts seem to prove that two factors are responsible for the heart damage in ancylostomiasis, the anemia and a toxic agent, dependent on the presence of the hookworm; in the majority of cases it is possible to compensate (temporarily?) the action of the second factor by curing the anemia, but a minority remains where this factor is predominant and exerts its myocardial damaging influence irrespective of the blood condition. No decision was reached as to whether this agent is a toxin or an allergin; the eosinophilia, said to be found frequently in ancylostomiasis, points toward the second possibility. Complete elimination of the hookworms, however, has to follow the antianemic treatment, preferably succeeded by prolonged iron medication, to get optimum and lasting results.

AUTHOR.

Evans, W.: Mitral Systolic Murmurs. Brit. M. J. **1**: 8, 1943.

The need is discussed for an evaluation of these murmurs in the diagnosis of heart disease, and for examining the distinctive feature which may identify the murmur with some precise cardiologic disorder. The murmurs are divided into three categories: irrelevant, innocent, and mitral incompetence. The discussion is brief, but very inclusive, and gives proper emphasis to the relative importance of this physical sign.

MCCULLOCH.

Dassen, R., and Fongi, E. G.: Hamman's Syndrome. Medicina, Buenos Aires **3**: 76, 1942.

A clinical case of Hamman's syndrome in a woman 23 years of age is described. The diagnosis is made and the basis to recognize it is given, showing its differences with pericarditis and acute coronary occlusion.

AUTHORS.

Moloney, W. C.: The Occurrence of Abnormal Capillary Fragility in the Newborn. Am. J. M. Sc. **205**: 229, 1943.

In a preliminary study of capillary resistance in the newborn, thirty-three (60 per cent) of fifty-five infants showed more or less abnormal capillary fragility.

This decreased capillary resistance disappeared as the infants became older.

Various factors influencing permeability of the capillary wall are outlined, and the possible relationship of abnormal capillary resistance to hemorrhagic disorders in the newborn is postulated.

AUTHOR.

Coburn, A. F., and Moore, L. V.: Salicylate Prophylaxis in Rheumatic Fever, J. Pediat. **21:** 180, 1942.

One hundred eighty-six young rheumatic subjects were observed before and following hemolytic streptococcal pharyngitis. Of forty-seven who received prophylactic doses of sodium salicylate, only one developed rheumatic fever. Of one hundred and thirty-nine untreated patients, fifty-seven developed rheumatic fever. These observations suggest that rheumatic fever can be prevented by the administration of salicylates during the respiratory infection and silent phase of the rheumatic infection. The mechanism appears to be the prevention of antigen-antibody precipitation.

KERSHBAUM.

Padilla, T.: Cardiovascular Syphilis in 1942. Medicina, Buenos Aires **3:** 24, 1942.

The clinical aspects of syphilis of the heart and aorta are studied. Four forms of syphilitic aortitis are pointed out: first degree, simple aortitis or not complicated; second degree, aortitis with dilatation which can become aneurysm; third degree, aortitis with aortic insufficiency; fourth degree, aortitis with obstruction at the ostium of the coronaries.

The high value (100 per cent positive) of the biologic reactions should be noted (Wassermann and Kahn) for the diagnosis of aortic syphilis in nontreated patients, and the importance of precocious and intensive treatment to impede the development of serious syphilitic aortitis.

AUTHOR.

Smith, K. S.: Cardiac Syndromes Complicating Diabetes and Their Treatment. Brit. Heart J. **5:** 1, 1943.

The evidence proving that diabetes conduces to early and severe arteriosclerosis, and, especially, coronary arterial disease and coronary thrombosis, has been reviewed.

The clinical features of forty-nine consecutive cases of diabetes associated with heart disease have been analyzed. The sexes were fairly evenly represented; the average age of the men was 62 years, and that of the women 61 years.

Hypertension was present in forty-four of the forty-nine patients (almost 90 per cent); in thirty-one instances the blood pressure was 180 mm. or more. As is usual in hypertension uncomplicated by diabetes the blood pressure frequently dropped swiftly and considerably on confining the patients to bed. Reasons were adduced for believing that hypertension in the diabetic was in some degree directly attributable to the metabolic fault.

A study was made of the manner in which angina of effort, spasmodic angina, coronary thrombosis, left ventricular failure, and congestive heart failure supervened in diabetics. Some case histories illustrating these events, and showing the relationship between the diabetic state and the cardiac development, have been summarized.

As a rule, patients with diabetes and some form of angina or heart failure were found to derive benefit from any necessary readjustments of regime or insulin dosage. Controlled observations were not, for obvious reasons, generally possible, but in a few patients, in whom this adjustment only was made, deterioration in the heart condition was replaced by improvement.

It has been concluded that, while the lives of patients with disease of the coronary artery are at serious risk, those of the "cardiac diabetics" are even more precarious. Coronary thrombosis in the diabetic is extremely hazardous.

Methods of treatment of cardiac complications in diabetes have been reviewed. The requirements of diet, fluid, insulin, glucose, and remedies directed to the heart

have been considered. The well-known principle that, in patients with heart disease, sudden reductions of blood sugar by diet or insulin are not well tolerated has been endorsed in the present study. In general, the use of insulin will be in such dosage as may be necessary to abolish acetonemia and reduce severe hyperglycemia. To use insulin to procure stabilization or exact control of the diabetes in patients with additional heart disease is to court disaster.

AUTHOR.

Shrader, J. C., Young, J. M., and Page, I. H.: Pyelograms in Patients With Essential and Malignant Hypertension. Am. J. M. Sc. 205: 505, 1943.

The retrograde pyelograms of 100 hypertensives and 100 normotensives were studied to ascertain whether hypertension was associated with any constant pyelographic variation. Those which seemed more common in hypertensives were renal pelves which were larger than average, and pelves whose position was lower than average. Intrarenal pelvis, incomplete rotation (renal torsion), right-angled ureteropelvic juncture, and bifid pelvis were no more common than in normotensive patients. Hypertension was not associated with any significant variation in the size of the pelvis to the size of the calices, the general configuration of the pelvis, the pelvic axis, nor the number or morphology of minor calices.

The incidence of hypertension in patients who exhibited easily recognizable renal abnormalities as demonstrated by retrograde pyelograms was 22 per cent. The average mean arterial pressure of patients with abnormal pyelograms was the same as the average mean pressure of those with normal pyelograms. The incidence of significant renal abnormalities in an unselected group of hypertensives was 19 per cent.

The retrograde pyelograms of patients with essential hypertension do not differ significantly from those of normotensives. The incidence of urographic abnormalities in an unselected group of hypertensives appears to be no greater than in normotensives.

AUTHORS.

Daley, R. M., Ungerleider, H. E., and Gubner, R. S.: Prognosis in Hypertension. J. A. M. A. 121: 383, 1943.

Hypertension is important for two reasons: as an indication of an underlying disease, and because of the deleterious effects of the elevated blood pressure itself. The mortality from heart failure and degenerative atherosclerotic changes of the large vessels, such as the coronary arteries, which result from long-standing duration of hypertension without regard to its degree, is far greater than the mortality from such causes as malignant nephrosclerosis and apoplexy, which can be attributed more directly to a decided elevation of the blood pressure. It is evident, therefore, that an important consideration in prognosis is the proper evaluation of the duration of the hypertension, apart from its degree. Since the degenerative atherosclerotic changes may occur in the absence of advanced arteriolar disease, it appears that the grading of hypertension solely by arteriolar changes (blood pressure levels and reactivity, retinal examination, pectoral biopsy), which indicate the degree and not necessarily the duration of hypertension, has certain shortcomings. The extreme variability in the level of the blood pressure, diastolic as well as systolic, dictates reserve in drawing conclusions from casual blood pressure readings. The range of blood pressure in subjects with hypertension may be determined most simply by employing the breath-holding pressor test to determine the "ceiling," and overbreathing for a short period as a depressor test to determine the lowest level to which the blood pressure may be expected to fall.

Left ventricular hypertrophy and atherosclerotic changes, particularly in the coronary vessels and the aorta, are invariable accompaniments of elevated arterial pressure of long standing, and are serviceable as prognostic guides. Hypertrophy of the left ventricle can be determined by means of x-ray study and electrocardiography, which also serve to reveal arteriosclerotic changes in the aorta and coronary arteries. The electrocardiogram is somewhat more sensitive than roentgen findings for early detection of left ventricular hypertrophy, employing criteria established by study of a large number of normal and hypertensive subjects. There is a marked increase in mortality with progression in the electrocardiogram toward an abnormal pattern.

Other considerations, including heredity, sex, age, and the presence of associated conditions such as renal disease, diabetes, and obesity, are important in estimating the life expectancy and the benefit which may be expected from therapeutic procedures available at the present time. The advent of several new therapeutic approaches offers real promise that hypertension may be brought under some measure of control, and therefore prognosis becomes of great practical importance, both as a standard by which to evaluate new therapeutic procedures, and also as an indication in the proper selection of cases amenable to various forms of therapy.

AUTHORS.

Lewis, R. N., Werle, J. M., and Wiggers, C. J.: The Behavior of the Spleen in Hemorrhagic Hypotension and Shock. Am. J. Physiol. 138: 205, 1943.

In nine experiments on dogs, the changes in areas of exteriorized spleens were studied by the method of Barcroft and Stephens during hemorrhage, posthemorrhagic hypotension, and hemorrhagic shock following reinjection of the blood which had been withdrawn.

In confirmation of previous reports, it was found that the spleen contracts rapidly and extremely during hemorrhage, the area being reduced by 50 per cent or more. In extension, it was found that during a period of prolonged posthemorrhagic hypotension the dog's spleen undergoes a further slow contraction, does not increase on reinfusion of the withdrawn blood, but remains contracted whenever the duration and intensity of the hypotension are sufficient to create dynamic and pathologic signs of shock. Similar changes occurred in plasmapheresis experiments.

In the dog, splenic contraction does not contribute to elevation or maintenance of arterial pressure by virtue of the increased resistance induced in the splenic shunt, but by augmenting venous return and cardiac output. The spleen is not an organ which withdraws blood from active circulation in hemorrhagic shock. When the spleen is found large and congested at autopsy, other factors must have operated.

AUTHORS.

Warren, J. V., and Stead, E. A., Jr.: The Effect of the Accumulation of Blood in the Extremities on the Venous Pressure of Normal Subjects. Am. J. M. Sc. 205: 501, 1943.

Venous tourniquets at a pressure of 85 mm. Hg were applied to the upper thighs of six normal subjects.

The application of these tourniquets caused a decrease in venous pressure in both the external jugular and antecubital veins. The average fall in venous pressure in the external jugular vein was 53 mm. of water. The average fall in venous pressure in the antecubital vein was 23 mm. of water.

The decrease in venous pressure from the application of tourniquets to the upper thighs is greater in the external jugular than in the antecubital vein, because the arm veins tend to collapse when the venous pressure is lowered. After the vein walls are in contact, further lowering of the venous pressure proximal to the point of collapse produces no further decrease in venous pressure in the distal portion of the vein.

AUTHORS.

Homans, J.: Vasomotor and Other Reactions to Injuries and Venous Thrombosis. Am. J. M. Sc. **205**: 313, 1943.

This is a classic discussion of the subject, expressing the author's own conception of the problem. It must be read to be appreciated, and the reading is well worth while.

MCCULLOCH.

Schill, E.: A Case of Spasm of the Vessels of the Respiratory Center With Secondary Lung Edema. Cardiologia **6**: 221, 1942.

A temporary spasm of the vessels supplying the breathing center, amenable to intravenously administered sodium nitrite, which well-nigh caused cessation of breathing, was accompanied with edema of the lungs in consequence of failing arterialization of the blood, and consequent poor nourishment of the heart muscles since the left half of the heart had been formerly damaged owing to hypertonia and previous thrombosis of the left coronary artery.

AUTHOR.

Cossio, P., and Fustinoni, O.: Angina Pectoris and Diaphragmatic Hernia. Rev. argent. de cardiol. **9**: 217, 1942.

The literature upon the nature of the painful crisis in diaphragmatic hernia is reviewed, and five personal observations are reported in which these crises were erroneously considered as due to angina pectoris of coronary origin, or myocardial infarct.

The error in diagnosis was made because of the pain characteristics (intensity, localization, irradiation, effectivity of nitroglycerin) and the appearance of a coronary wave in the electrocardiogram, or because of an apparently irreducible cardiac insufficiency.

A few facts are pointed out which may avoid this diagnostic error. The electrocardiographic alterations are explained as due to inflammatory or mechanical action of the hernia upon the pericardial surface of the heart. The cardiac insufficiency is considered to be a consequence of vitamin B_1 deficiency, or of anemia which may follow circulatory or inflammatory alterations of the gastric muscosa.

It is maintained that the pain attacks are, at least sometimes or partly, of cardiac origin. It is appropriate, therefore, to speak of angina pectoris in diaphragmatic hernia, as well as in anemia, aortic stenosis, and aortic insufficiency.

AUTHORS.

Edwards, E. A., and Edwards, J. E.: The Venous Valves in Thromboangiitis Obliterans. Arch. Path. **35**: 242, 1943.

Examination of the blood vessels of the lower extremities shows that thromboangiitis obliterans damages the venous valves extensively and seriously. The lesions

involving the valves are part of the changes in the blood vessels in general, first, inflammation; second, thrombosis; and third, dilatation secondary to the obstruction by the inflammation or thrombosis.

The valves may be disrupted by the inflammation. Their excursion may be limited by their involvement in the inflammatory exudate in the valve or in the vessel wall, or by the formation of adhesions.

In obstructive thrombosis the valve is destroyed by the organization and recanalization, any remaining portions being incorporated in the walls of the channel or channels. In mural thrombosis the cusps may be incorporated in the organizing tissue, or their excursion may be limited by thickening and adhesion.

The dilatation of the veins distal to areas of obstruction is associated with relative incompetence of the valve. The growth of reparative tissue often additionally thickens the cusps and makes them rigid. The thesis is presented that this may be but one part of a widespread proliferative change in thromboangiitis obliterans secondary to the obstruction of the blood vessels.

AUTHORS.

Edholm, O. G.: The Compensatory Mechanism of the Splanchnic Circulation During Changes of Posture. J. Physiol. **101:** 1, 1942.

The mechanisms responsible for the fall in blood pressure in the feet-down position have been examined in the cat. Evisceration does not abolish the fall, but diminishes the vascular compensation. Removal of the liver, with or without evisceration, almost abolishes the fall of blood pressure in the feet-down position. The fall in blood pressure is due to the collection of blood in the liver, not in the splanchnic region although this area is partly responsible for the compensation following this fall. The recovery of blood pressure on restoring the animal to the horizontal position is due to the return to the right side of the heart of the blood which had accumulated in the liver.

KERSHBAUM.

Currens, J., and Barnes, A. R.: The Heart in Pulmonary Embolism. Arch. Int. Med. **71:** 325, 1943.

A study of the heart was made in cases in which pulmonary embolism occurred. It is noted that the size of the heart in the surgical group of cases in which pulmonary embolism develops, and the surgical group in which pulmonary embolism does not develop, is essentially the same. Since chronic valvular defects and disease of the pericardium were excluded as causes of cardiac enlargement, this evidence indicates that hypertension does not predispose to pulmonary embolism among surgical patients. The heart was examined in thirty cases in which pulmonary embolism occurred, and evidence of acute infarction was found in five. In four of these cases, no significant obstruction was found in the coronary arteries, but in the fifth case there was fresh coronary thrombosis. One case in which there was prolonged shock is presented. In this case there was acute infarction involving the posterior wall of the left ventricle, without coronary thrombosis. The electrocardiographic differentiation of infarction of the posterior wall of the left ventricle, and pulmonary embolism, is illustrated and discussed, and the value of the chest leads in differentiating the two is stressed. The mechanism of the production of electrocardiographic changes is discussed, and a possible explanation for angina pectoris, which occasionally occurs in pulmonary embolism, is suggested.

AUTHORS.

Mayerson, H. S.: Roentgenkymographic Determination of Cardiac Output in Syncope Induced by Gravity. Am. J. Physiol. 138: 630, 1943.

Individuals who can stand quietly for at least twenty minutes show insignificant changes in the stroke and cardiac outputs during the standing period as determined by the roentgenkymographic method. Fainters show a marked decrease in these functions under the same conditions. If no marked movement occurs, the stroke output just before syncope is 25 to 35 per cent less than at the beginning of the standing period, while the cardiac output has diminished 21 to 43 per cent. The development of syncope in quiet standing is primarily due to the absence of adequate muscular contraction which results in a diminished venous return. The vasomotor failure is secondary.

AUTHOR.

Lowsley, O. S., and Cannon, E. M.: Aneurysm of the Renal Artery. J. A. M. A. 121: 1137, 1943.

Aneurysm of the renal artery is a rare clinical pathologic entity. Only seventy-five cases have been reported to date, including a case of true aneurysm diagnosed preoperatively and presented here.

A congenital defect in the wall of the renal artery, particularly at its bifurcation, is a hypothetic factor in the etiology of aneurysm. It is questionable whether trauma per se produces renal aneurysm.

Only twelve of the seventy-five reported cases were suspected prior to operation or death.

True aneurysm is usually asymptomatic. A few patients have complained of pain in the flank. The cardinal symptoms of false aneurysm are hematuria, pain, and tumefaction in the flank. The pathognomonic signs, pulsation and a systolic bruit, have been present in seven cases. The presence in the x-ray film of a ringlike shadow, with a dense periphery disrupted in one portion, and a rarefaction of the center in the kidney or hilar region, is suggestive of a renal aneurysm.

The treatment is surgical. In the literature, all patitents presenting symptoms who were not operated on died. Of the twenty-nine patients subjected to nephrectomy, twenty-six survived. Of thirty-seven patients who underwent operation, eight died, an operative mortality of 21 per cent.

AUTHORS.

Darrow, D. C., and Miller, H. C.: The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate. J. Clin. Investigation 21: 601, 1942.

Evidence is presented that cardiac lesions were produced by prolonged injections of desoxycorticosterone acetate in rats. The dose of DOCA was 1, 2, and 4 mg. daily, and the observations were made over a period of thirty to forty days. Necrosis of the myocardial fibers and replacement by fibroblasts were produced by these repeated injections. Pyridoxin intake did not influence the production of the lesions nor did a low intake of thiamin aggravate them. Diets low in potassium produced lesions in the heart which could not be distinguished from that produced by the repeated injections of DOCA. Only a suggestive lowering of the potassium in the cardiac muscle was found in contrast to a more definite lowering of the potassium in the skeletal muscle.

The cardiac lesions produced by injections of DOCA or diets low in potassium can be prevented by addition of potassium chloride to the drinking water. Deficit of body potassium is apparently essential for the production of these lesions.

GRACE M. ROTH.

Lebowich, R. J.: Chemotherapy of Experimental Streptococcic Pericarditis: A Comparison of Sulfanilamide and an Acetylated Derivative of 4,4′-Diaminodiphenylsulfone Hydrochloride in the Treatment of Experimental Beta Hemolytic Streptococcus Pericarditis in the Rabbit. Arch. Path. 35: 253, 1943.

It has been shown for the strain of beta hemolytic streptococcus investigated that an acetylated derivative of 4,4′-diaminodiphenylsulfone hydrochloride exercises a distinctly beneficial effect on the natural course of experimental beta hemolytic streptococcus pericarditis in rabbits. It considerably increases the number of cured survivors in comparison with their complete absence in the sulfanilamide-treated group, and definitely prolongs the average duration of life beyond that of the control and that of the sulfanilamide-treated group. The most effective results were obtained in a group of fifty rabbits whose treatment was initiated twelve hours after the production of pericarditis; forty-nine of these animals were cured. The incidence of survivors and the prolongation of life are definitely related to the time of starting treatment.

The toxicity of this compound is of a relatively low order.

The results are on a scale sufficiently large to indicate that the acetylated derivative of 4,4′-diaminodiphenylsulfone hydrochloride is far superior to sulfanilamide in its therapeutic effect on beta hemolytic streptococcus infection of the pericardium as observed in rabbits.

AUTHOR.

Gefter, W. I., and Leaman, W. G., Jr.: The Use of Ouabain in Rapid Cardiac Arrhythmias. Am. J. M. Sc. 205: 190, 1943.

One intravenous dose of ouabain produces a statistically significant reduction in ventricular rate and is an effective method of treating rapid cardiac arrhythmias of auricular origin. It is relatively ineffective when the mechanism is that of a simple tachycardia or when complicated by severe infection.

When combined with one oral dose of digitalis, intravenous ouabain is an effective aid in producing full digitalization.

AUTHORS.

Goldsmith, G. A., and Cordill, S.: The Vasodilating Effects of Nicotinic Acid (Relation to Metabolic Rate and Body Temperature). Am. J. M. Sc. 205: 204, 1943.

The administration of nicotinic acid produced no significant change in metabolic rate or body temperature before the appearance of the characteristic skin reaction. The vasodilatation, therefore, does not seem to be compensatory to increased heat production. Available evidence at the present time suggests that the vasodilator response is due to a local effect on the arterioles in the skin.

AUTHORS.

Book Reviews

THE EPIDEMIOLOGY OF RHEUMATIC FEVER AND SOME OF ITS PUBLIC HEALTH ASPECTS: By John R. Paul, M.D., Professor of Preventive Medicine, Yale University School of Medicine, and other contributors; second edition, 1943. Printed by the Metropolitan Life Insurance Company for the American Heart Association. 163 pages, 31 illustrations.

Of the various chronic infectious diseases of the United States, rheumatic fever now ranks behind only tuberculosis and syphilis as a cause of illness and death. Judging from the trend in recent mortality and morbidity statistics, one can venture the prediction that within another half century rheumatic fever will occupy first place in this group of diseases. For this reason and also because of the importance of the disease in military medicine, a review of the factors which control its incidence and spread is particularly timely at present. Dr. John Paul's book meets this need in a thoroughly admirable fashion. In the brief space of 150 pages he has covered a great amount of material, and has summarized all of the important studies of the past two decades. These recent studies have been well integrated with the historical aspects of the disease.

The tone of the book is judicial throughout. Both sides of controversial questions are considered in a critical but thoroughly unprejudiced manner. The recent work bearing on the relationship of hemolytic streptococcal infections to the disease is reviewed, and the author concludes that although there is rather overwhelming evidence to indicate some relationship, such evidence does not yet permit one to draw the conclusion that the hemolytic streptococcus is the only noxious agent concerned.

A large portion of the book is devoted to a discussion of various host factors, including age, sex, and racial predisposing factors, as well as the influence of living conditions and climate. There is also a comprehensive discussion of rheumatic families; the author cites the evidence which indicates that contagion alone cannot account for the prevalence of the disease in such families, and, therefore, states that hereditary susceptibility must be assumed.

The last two chapters deal with possible future Public Health procedures, by D. D. Rutstein, of the Cardiac Bureau, New York State Department of Health, and with general principles concerning the care of chronic rheumatic fever and rheumatic heart disease, by T. Duckett Jones of the Good Samaritan Hospital in Boston. These chapters are, likewise, thoroughly modern, and critically written.

The style of the book is unusually readable, and the material is presented in such a clear fashion that it can be readily assimilated by a second-year medical student, or even by a layman who has the barest acquaintanceship with medicine. This is not to be taken to mean that the book is written primarily for such persons. There is a wealth of material which can be profitably read by general practitioners, internists, and Public Health physicians.

Dr. Paul's book is not for sale; it was published for the American Heart Association, and the Metropolitan Life Insurance Co. has generously borne the cost of publication. Physicians whose special interests and activities entitle them to the book may obtain it free of charge by writing to the American Heart Association. Copies have already been sent to hospitals, camps, libraries, and certain individual officers in the United States Army.

TINSLEY R. HARRISON.

PHYSIOLOGY IN AVIATION: By Chalmers L. Gemmill, M.D., Commander, M.C., U.S.N.R., Associate Professor of Physiology, Johns Hopkins University School of Medicine, Instructor in Physiology, School of Medicine, Naval Air Station, Pensacola, Fla. Charles C Thomas, Springfield, Ill., 1943, 124 pages, 18 figures, 18 tables, $2.00.

The author has been in charge of the course of lectures on aviation physiology at the School of Aviation Medicine of the Naval Air Station at Pensacola, Fla. This little book contains the material covered in the lectures, and offers a clear and simple summary of the basic physiology necessary for an understanding of the reactions of men exposed to the hazards of altitude.

The book is intended for beginners in the subject and seems well adapted to the purpose. Advanced students will regret the lack of a bibliography, and some may question whether subject matter such as this should be presented, even to beginners, with so little hint of the difficulties and doubts involved.

ISAAC STARR.

ANOXEMIA CARDIACA, EXPERIMENTAL Y CLINICA: By Dr. Moises Sloer, Profesor Adjunto de Patologia, Rosario. Tesis de Profesorado, Rosario, Argentina, 1942, 69 pages.

The author reviews the chief studies on cardiac anoxemia, from Rothschild and Kissin, to Levy and co-workers. Experimental and clinical observations follow. Experiments on dogs with different gas mixtures show that *anoxemia* causes increase of respiratory rate, hypertension, and tachycardia. These changes are reversed by breathing mixtures containing less than 3 to 4 per cent of oxygen. These mixtures also cause many electrocardiographic changes, such as nodal rhythm, A-V block, inversion of T, and deviation of S-T from the base line.

Clinical observations were made on thirty cases, including normal subjects, doubtful cases, and heart patients. *Anoxemia* caused increased frequency of respiration and lowering of the T wave of the electrocardiogram in the first two groups; everything else remained practically unchanged. The height of the T wave decreased more in doubtful heart cases than in normal persons. The administration of pure oxygen after anoxemia brings back normal conditions. Anoxemia causes the following electrocardiographic changes in heart patients: tachycardia; no changes of either P or P-R; decrease of R; flattening or inversion of T; and displacement of S-T from the base line. In general, the changes were greater in this group than in the two others. The author finds in these changes a confirmation of the anoxemic theory of angina pectoris. He does not believe, however, that electrocardiographic changes can be used as a test of coronary insufficiency.

Therapeutic use of oxygen is recommended in all heart cases when coronary insufficiency is present.

A. LUISADA.

EL PULSO VENOSO NORMAL: By Agustín Caeiro, Córdoba, Argentina. S. de Amorrortu, Buenos Aires, 1942, 148 pages, 57 illustrations.

This booklet reviews in a clear and complete way the studies on jugular vein tracings from Wedemeyer to Orías. After discussing the factors which regulate the venous circulation, the mechanism of production of the different waves is described. In one of the most interesting chapters the author reports his own studies on the velocity of the waves in the venae cavae of dogs. From the clinical and experimental observations on venous tracings, the author concludes that each wave of the venous pulse is the result of the combined action of changes in the volume of the

vein, changes in the pressure, and changes in the velocity of the venous blood flow. In another chapter there is an accurate description of the time relations between the waves of the jugular tracing and those of other tracings. This will be of use to students of the circulatory apparatus. At the end of the book there is an extensive summary in both Spanish and English.

ALDO LUISADA.

Errata

In the article entitled "The Effect of the Intravenous Administration of Lanatoside C Upon the Output, Diastolic Volume, and Mechanical Efficiency of the Failing Human Heart," by John S. LaDue and George Fahr, which appeared in the March, 1943, issue of the JOURNAL, volume 25, page 344, the following corrections should be made: In Fig. 2 the value for V_D should be 885.3 cm.^{3}, and, for V_S, 844.4 cm.^{3}; in Fig. 3, V_D should be 738.7 cm.^{3}, and V_S, 691.4 cm.^{3}

In the paper by Dr. Henry I. Russek, entitled "Blood Pressure in the Aged," which appeared in the July, 1943, issue of the JOURNAL, volume 26, page 11, the sentence under Table IV, which reads "Percentage variation from unexpected mortality" should be "Percentage variation from expected mortality."

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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